Volume XVI, Number 10 Monday, July 20, 2009

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

Vitamin D's Laboratory Magazine Trifecta

WITH APOLOGIES TO FANS OF HORSE RACING, I OBSERVE THAT THE SUBJECT of Vitamin D has just achieved a noteworthy trifecta in laboratory medicine. In recent months, at least four of the bigger controlled-circulation magazines widely-read by laboratory professionals have run major cover stories on Vitamin D and Vitamin D testing.

It is not often that a single topic becomes a headline story for the majority of controlled-circulation laboratory magazines within such a tight window of time. That makes this development noteworthy as a sign of an important industry trend. Because these controlled-circulation magazines are advertising-driven, they want topics that will draw eyeballs (and attract related advertisers). So their decision, somewhat independently of each other, to headline stories about Vitamin D testing, means that their market research has uncovered strong interest in this topic among their readers.

Using the amount of news space devoted to a single topic as a way to identify trends is an accepted practice. Those readers who share my age and perspective, will recall a mega-best-selling book in the early 1980s by the title of "Megatrends." The author, John Naisbitt, calculated the amount of news space given to certain topics by newspapers, magazines, and television news broadcasts. He correctly understood that, as news reporters increased their coverage of specific topics, this would be an early marker for a trend that would become highly influential in society.

For the record, back in 1982, Naisbitt correctly called these three trends. One, a rapid transition from the industrial age to the information age. Two, the dominance of the global economy, requiring nations to open their national economies to global trade. Three, networks as the process which would open up commercial and public access to goods, services, and information across the globe. (Today, we have the Internet as the ultimate network.)

If you follow my chain of thought, the recent laboratory industry magazine coverage of Vitamin D testing is the marker for a major trend, still in its early stage. I will make a stab at a prediction. The physician and consumer hubbub that we now see over Vitamin D levels is the visible sign of a shift in both physician and consumer behavior. They are shifting from reactive healthcare to proactive healthcare. Vitamin D is the current example because it is relatively simple for consumers to cure a deficiency with an easy-to-take supplement. TDR

All-Star Vitamin D Panel Looks at Lab Challenges

Special EXECUTIVE WAR COLLEGE session inspires major stories in *CAP Today* and *Clinical Lab News*

CEO SUMMARY: ***Need proof that the issues surrounding today's Vitamin 25(OH) D are of keen interest to laboratory professionals? Not only did the EXECUTIVE WAR COLLEGE's in depth sessions on Vitamin D draw a large audience and enthusiastic participation by attendees, but within weeks, two of the lab industry's most-watched magazines published headline stories about Vitamin D issues, built in-part around interviews with the All-Star Vitamin D panelists, as well as several other lab experts.***

VITAMIN D IS THE LABORATORY TEST OF THE HOUR in our society. Media stories regularly trumpet new clinical studies which implicate Vitamin D insufficiency as a factor in a growing number of diseases and medical conditions.

Patients and physicians have responded by ordering more Vitamin D tests. In each of the last three years, the volume of Vitamin D tests performed in the United States has skyrocketed upward. In many labs, Vitamin D now ranks as one of the most-frequently ordered tests.

But all has not been well in the world of Vitamin D testing. Laboratory experts have been reticent to speak openly and in detail about a host of issues and problems—some with the potential to affect clinical care and expose patients to less-than ideal care.

Thus, it was no surprise that, at this year's EXECUTIVE WAR COLLEGE ON LAB AND PATHOLOGY MANAGEMENT, two sessions on Vitamin D testing generated the most enthusiastic audience interest and participation. First was a presentation by Bruce Hollis, Ph.D., Professor of Pediatrics and Neonatology at the **Medical University of South Carolina** in Charleston, South Carolina.

Hollis developed the proprietary technology that is part of the most widely-used Vitamin 25(OH) D immunoassays. He reviewed the history of past and recent clinical studies involving Vitamin D. An ardent believer in the value of Vitamin D for maintaining optimal health, he provided evidence and made persuasive arguments that convinced many in the audience. This editor was told by several

THE DARK REPORT Intelligence Briefings for Laboratory CEOs, COOs, CFOs, and Pathologists are sent 17 times per year by The Dark Group, Inc., 21806 Briarcliff Drive, Spicewood, Texas, 78669, Voice 1.800.560.6363, Fax 512.264.0969. **(ISSN 1097-2919.)**

R. Lewis Dark, Founder & Publisher. Robert L. Michel, Editor.

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).

Executive War College attendees that they left the hotel at the end of the session and went to a pharmacy across the street to purchase Vitamin D3 supplements (which Hollis recommends over D2 supplements)!

All-Star Vitamin D Panel

Immediately after Hollis' presentation was the All-Star Vitamin D Panel, populated by a group of international luminaries in Vitamin D testing. Along with Bruce Hollis, M.D., the other panelists were:

- Julian Barth, Ph.D.
  Consultant in Chemical Pathology & Metabolic Medicine, ***The General Infirmary at Leeds****, Leeds, West Yorkshire, United Kingdom*
- Russell Grant, Ph.D.
  Strategic Director, National Office of Quality & Science, ***Esoterix, Inc.****, Burlington, North Carolina*
- L.V. Rao, Ph.D.
  Director of Core Laboratories, ***UMass Memorial Medical Center****, Worcester, Masssachusetts*
- Andre Valcour, Ph.D.
  Vice President, Director of Laboratories, ***Laboratory Corporation of America****, Burlington, North Carolina*

During a lively one-hour session, this panel discussed, in polite, but candid detail, contemporary issues and problems with Vitamin D test methodologies, including immunoassay and mass spectrometry. The panel commented on how and why some current practices in laboratory testing for Vitamin D can be—at a minimum—unhelpful to clinicians, and at a maximum, have the potential to negatively affect appropriate diagnoses and treatments for individual patients.

This public discussion was a first in the laboratory industry because it directly addressed problems and challenges that confront any laboratory offering Vitamin D testing and competing for outreach lab testing business. The relevance and new ground covered by this EXECUTIVE WAR COLLEGE All-Star Vitamin D Panel is confirmed by a subsequent development.

Within weeks of the EXECUTIVE WAR COLLEGE, both *CAP Today* (published by the **College of American Pathologists**–CAP) and *Clinical Laboratory News* (published by the **American Association of Clinical Chemistry**–AACC) interviewed these panelists (and other lab experts) and headlined their respective editions with their coverage, based in part, from this All-Star Vitamin D Panel.

Readers of THE DARK REPORT who want to access this material should look for "Vitamin D Intrigues, But Not a Done Deal" in the June 2009 issue of *CAP Today* (Vol. 23, No. 6) and "Vitamin D Testing—What's the Right Answer? Labs Grapple with Confusing Analytics, Evidence" in the July 2009 issue of *Clinical Laboratory News* (Vol. 35, No. 7).

Vitamin D Lab Test Practices

In anticipation of the publication of these stories, THE DARK REPORT has withheld its intelligence briefings and analysis of the Hollis session and the All-Star Panel. On the following pages, we provide the insights and experience of L.V. Rao, Ph.D., at UMass Laboratories, as he and his team worked through the challenges of offering clinicians both the FDA-cleared immunoassay methodology and their home brew tandem mass spectrometry (LC-MS) assay for Vitamin 25(OH) D.

During the All-Star Panel, Rao shared the data generated by the UMass Lab studies done as the LC-MS assay was developed and evaluated against the lab's existing chemiluminescence assay and the LC-MS Vitamin D assay offered by **Mayo Medical Laboratories**. That data is presented on pages 5-10.

Rao offers pathologists and lab directors invaluable insights into the issues associated with Vitamin D methodologies. Of equal importance, he shares his lab's experience working with physicians, along with the practical solutions his laboratory developed in response to the feedback it got from its physician-clients. TDR

UMass Lab's Experience With Vitamin D Methods

Along with the established immunoassay, UMass Lab developed a home brew LC-MS assay

CEO SUMMARY: As it developed a home brew mass spec assay for Vitamin 25(OH) D to meet the request of some client physicians, the laboratory at the University of Massachusetts Medical Center quickly recognized several challenges. First, there were fundamental differences in the numbers generated on the same population by the internally-developed LC-MS assay compared to the established immunoassay. Second, physicians were not alert to these differences when results were reported to them.

IN TODAY'S HYPERACTIVE MARKET for Vitamin 25(OH) D testing, the typical clinical laboratory faces at least two challenges as it tries to "get it right" for the physicians and patients it serves.

First, the FDA-cleared immunoassay (IA) that has been in widespread use for almost two decades—and is familiar to most physicians—has an aggressive new competitor: a Vitamin 25(OH) D home brew assay that uses tandem mass spectrometry. Results produced by these different methodologies often do not correlate.

This has caused confusion among clinicians who have long experience with the Vitamin 25(OH) D results produced by the immunoassay method, but may not appreciate how and why the Vitamin D result produced by tandem mass spec can differ from the immunoassay.

Second, labs performing these different methodologies report their results using similar reference ranges. Across the laboratory testing industry, there is neither validation of reference ranges nor an effective effort to educate clinicians about this situation. Not surprisingly, clinicians can often be confused—particularly those clinicians who use multiple labs because of managed care contracts. And, if clinicians are confused, this raises the possibility that their patients may not get a proper diagnosis nor the appropriate treatment for their condition.

In New England, resolving these two issues in Vitamin 25(OH) D testing created significant clinical challenges for the laboratory at the **University of Massachusetts Medical Center**. This was the subject of a fascinating case study at the recent *Executive War College on Laboratory and Pathology Management* in New Orleans.

Different Test Methodologies

It was presented by L.V. Rao, Ph.D., who is Director of the Core Laboratory and Immunology at the UMass Laboratory. Rao described how his lab dealt with the requests by some client physicians to provide Vitamin 25(OH) D results by tandem mass spectrometry assay and not the widely-used chemiluminescence immunoassay.

"At UMass, we faced a practical problem with important clinical implications," stated Rao. "Most all our clinicians are quite comfortable with the long-established chemiluminescence assay (CIA) for Vitamin

25(OH) D. UMass offers the **Diasorin** CIA. But over the past year, we had several key clients ask us to provide them with a Vitamin 25(OH) D assay by tandem mass spectrometry (LC-MS).

"As we took the steps to develop an in-house tandem mass spec assay to meet the request of these physicians, we faced a number of difficult decisions centered around two primary issues," he said. "One, the immunoassay method and the mass spec method do not naturally correlate, as each typically produces a unique Vitamin D number from the same sample.

"Two, it is a reality in clinical practice today that the large majority of physicians are familiar with the results and reference ranges for the immunoassay method," Rao added. "Originally cleared by the FDA in 1993, the immunoassay has been around for almost two decades. Even today, it is the most widely-used method by the largest number of laboratories.

➤Significantly Different

"Therefore, if our lab was to report Vitamin 25(OH) D results by our home brew tandem mass spec method, how would we ensure that the clinician understands that our mass spec result and reference range are often likely to be significantly different numbers than if this same patient's sample had been tested by the immunoassay method?" he asked.

Here is what makes the experience of the UMass Lab of high interest to other labs evaluating both methodologies for Vitamin 25(OH) testing. As it developed its internally-developed tandem mass spec assay, UMass recognized the potential for clinicians to treat the reported LC-MS results and reference range as equivalent to those of the Vitamin D immunoassay method. If that happened, it might negatively affect patient care. Avoiding this dilemma proved to be a complex challenge for UMass.

"Today, labs have a number of methods available to measure for Vitamin 25(OH) D" said Rao. "These include the classic radioimmunoassays, ELISA 96-well direct assays, chemiluminescence assays, HPLC-UV, and HPLC-MS.

➤Clinical Studies Of Vitamin D

"In the past two decades, the immunoassays—specifically radioimmunoassays or chemiluminescence assays—have been used in the vast majority of clinical studies worldwide to define what is normal circulating 25-hydroxy levels," he observed. "These range from the Harvard cohort studies, such as the Health Professionals Follow-Up Study (HPFS), to the Women's Health Initiative (WHI) and the National Health and Nutrition Examination Survey (NHANES).

"In recent years, expanded use of tandem mass spec for Vitamin 25(OH) D testing has stimulated many publications in laboratory medicine literature," he continued. "Collectively, these publications show that there are some correlations, some agreement, and some controversy when the Vitamin D immunoassays are compared with the LC-MS assays for Vitamin D.

"Some published findings show substantial agreement between the two methods," explained Rao, "while other published findings show quite different results generated by these two methods. This is caused by many parameters which are not thoroughly understood.

➤Explaining The Differences

"Could these differences be due to the assay itself? To variations in performing the assay? Or how the matrix is used?" he asked. "The point here is not enough is understood about how and why the immunoassay method and the mass spec method for Vitamin D generate different answers."

Having established this context about some important differences between the immunoassay method and the mass spec method for Vitamin 25(OH) D, Rao discussed the steps taken by the UMass laboratory to evaluate the mass spec method and prepare to offer it for clinical use.

"In the past few years, our volume of Vitamin D testing increased dramatically,"

recalled Rao. "Go back three or four years ago. At that time, UMass Labs did maybe 300 to 400 Vitamin 25(OH) D tests per month. Right now we perform more than 11,000 tests per month!

Successful Lab Outreach

"Another factor is that our laboratory outreach program is successful at generating new clients," he continued. "Thus, many of our new client-physicians have recent experience using other labs in their medical practice. In the past year, a few of these physicians emphatically requested that UMass perform Vitamin D by LC-MS method.

"Our initial strategy was to accommodate these relatively few physicians in our outreach program by referring their Vitamin D specimens to **Mayo Medical Laboratories**," Rao stated. "Mayo performs the LC-MS method. That seemed like a good solution, until we compared those LC-MS results for our Massachusetts population against the results we generated by our CIA method.

"As you can see from table 1 [sidebar on page 8]," he continued, "there are significant differences in the reference range of our CIA and the Mayo LC-MS assay. There are also significant differences in how each assay method categorizes our Massachusetts population as Vitamin D deficient.

"The data you see draws from January-February 2009," noted Rao. "First, you will see the differences in the reference ranges of UMass, where above 30 is considered sufficient and Mayo, which uses above 25 as sufficient.

"Next, compare the distribution of the population results. By our CIA method, 68.7% of 16,000 patients were insufficient, under 30," he said. "But the same population—based on 4,000 tests during those same two months—when tested by Mayo's LC-MS method and using the cutoff of 25, classifies only 28.2% percent as Vitamin D deficient.

"That shows a significant difference," explained Rao. "It also presents pathologists and laboratory scientists with a question that cuts to the core of laboratory medicine. If you are a physician, which test methodology for Vitamin D do you use? As this table of actual results demonstrates, depending upon which method is used, the physician can classify somebody as deficient or not deficient. In turn, that drives the decision to treat, or not to treat.

"Next, we looked at what levels of D2 were detected from those 4,000 LC-MS results," Rao commented. "That is table 2, [see sidebar on page 8]. Almost 75% of the patients had no detectable levels of D2. About 12.5% of patients were at the minimum detectable levels of D2, 4 to 10. The remaining 13% of patients had D2 measurements of between 11 to 162 nanograms per liter. These findings told us that, with our Massachusetts population, around 87% have no or very little amounts of D2 to be detected separately.

Create In-House LS-MS Test

"As we performed these population studies, the volume of LC-MS requests continued growing," recalled Rao. "That encouraged us to decide, 'Let's handle these LC-MS requests with our own in-house assay. We have a toxicology department and we can double up our own assay.'

"As we established our LC-MS assay for Vitamin 25(OH) D, it coordinated very well with the Mayo Medical Lab results," he continued. "Next we measured about 600 samples simultaneously with both our LC-MS and the immunoassay method. This data is shown in table 3 [see sidebar on page 10].

"The data showed an fairly acceptable correlation (r=0.80), but with significant bias (approximately 40%)," noted Rao. "Informed by this information, we were concerned that the referring physicians who wanted Vitamin 25(OH) D by LC-MS may not understand the fundamental differences produced by this methodology versus immunoassay."

"We then visited several endocrinologists who had requested us to do their

UMass Labs Compares Vitamin D Methods: Immunoassay, Mass Spec on Same Population

Table One:

Vitamin D Deficient Population in Massachusetts (Jan-Feb 2009)

Liaison CIA (Performed at UMass)			LCMS (Performed at Mayo)		
Range	No. Tests	%	Range	No. Tests	%
<10	1,151	7.1%	<10	132	3.2%
10–30	9,844	60.7%	10–25	1,047	25.0%
30–100	5,217	32.2%	26–80	2,992	71.4%
>100	4	0.0%	>80	18	0.4%
	16,216	100.0%		4,189	100.0%
	deficient:	**67.8%**		**deficient:**	**28.2%**

This table shows how the two Vitamin 25(OH) D methods, as reported by the performing labs, differed in classifying the same population as deficient.

Table Two:

D2 Assessment of Massachusetts Population (Jan-Feb 2009)

This table reproduces the D2 results from UMass Lab's testing by its home brew LC-MS Vitamin D assay. Dr. Rao notes that 87% of his Massachusetts population has little or no amounts of D2 to be detected separately.

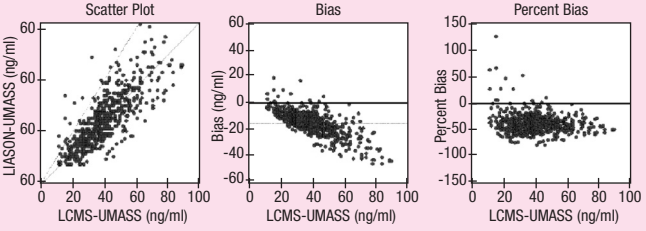
D2 Level	#	%
>4.0 ng/ml	3,116	74.4%
4–10 ng/ml	525	12.5%
11–162 ng/ml	**548**	**13.1%**
	4,189	100.0%

Table Three:

LCMS v. CIA Comparison At UMass Laboratories

Alternate (Quantitive) Method Comparison

X Method: LCMS-UMASS Y Method: LIAISON-UMASS



Regression Analysis

	Deming	Regular
Slope:	0.629 (0.595 to 0.663)	0.549 (0.515 to 0.583)
Intercept:	–0.8 (–2.3 to 0.7)	2.4 (1.0 to 3.9)
Std Err Est:	6.5	6.4

Corr Coef (R):	0.7980
Bias:	–15.8
X Mean ±SD:	–40.4 ± 15.4
Y Mean ±SD:	–24.6 ± 10.6
Std Dev Diffs:	9.4

95% Confidence Intervals are shown in parentheses

When it ran 600 samples simultaneously by chemiluminescence and by its home brew LC-MS assay, UMass Labs determined that the two assays had acceptable correlation (r=0.80). However, the bias (approximately 40%) had the potential to be unrecognized by physicians, who may often not understand fundamental differences between the two Vitamin D testing methodologies.

Vitamin D testing by LC-MS," he said. "We asked them just a few questions, such as: 'Are you and the majority of physicians in your group aware that there are differences in the methodologies of Vitamin D testing? Did you know about this bias that we see between the two methodologies?'

"Once these endocrinologists saw the comparative data between the two methods of Vitamin D testing, they were surprised," he added. "They told us that, because different laboratories give them essentially the same reference range—regardless of the methodology—they would not expect to see such a distinctly different bias in the results produced by the IA and LC-MS methods."

How Docs Use D2

Because endocrinologists typically see patients referred by primary care providers (PCPs), Dr. Rao and his UMass colleagues were intrigued to know how both PCPs and endocrinologists might or might not be using D2 levels. "Our next question to the endocrinologists was "Do you get a patient referral because the PCP sees a D2 level reported as 'undetectable' and, possibly because of confusion about the significance of this number, then decides to refer the patient on to the specialist?'

"Their answer was not what we expected," Rao went on. "The endocrinologists told us that the vast majority of questions they get about low Vitamin D levels actually come from patients who have direct access to their laboratory test reports. These patients see the 'undetectable' D2 result on their test report and ask their doctor 'Am I vitamin D deficient?'

"Informed by these insights, we asked if there would be specific advantage in their clinical practice to know the D2 level compared to the total Vitamin 25(OH) D level reported by immunoassay method," recalled Rao. "Every doctor told us that, for patient screening purposes, there is no specific advantage to having the D2 and D3 subtotals reported along with a total Vitamin D. However, when a physician is monitoring a patient taking D2 therapy, then it would be appropriate to know the D2 level of that patient.

Educating Physicians

"This interaction with our client physicians helped us educate those physicians about the issues in using the two methods for Vitamin 25(OH) D testing," observed Rao. "However, in the larger game, it leaves us with an ongoing issue.

"We are a laboratory now offering clinicians the option of Vitamin 25(OH) D by the long-established, FDA-cleared chemiluminescence assay and by our home brew LC-MS assay," he noted. "We know and understand the differences in the results and the reference ranges we provide for each method.

"But a large number of physicians in practice today remain unaware that these important differences exist between the two methodologies," continued Rao. "As a result, the potential exists for these clinicians to make an inaccurate diagnosis and thereby possibly fail to provide the most appropriate treatment to the patient. As a laboratory, we would like to eliminate that imprecision, but there is no help from the national literature.

"What is missing to help clinicians—and the laboratories which serve them—are specific guidelines and agreements published in the broader clinical community regarding the appropriate clinical intervals of Vitamin D," offered Rao. "The literature provides no consensus on a specific level of 25-hydroxy indicator of Vitamin D deficiency.

"Further, the majority of the many studies published over the years used radioimmunoassays and chemiluminescent assays," he observed. "Recommended optimum levels have come from these studies. But this situation does not provide effective guidance to labs and physicians for use of the LC-MS method in determining Vitamin D levels.

"This is the gap, so to speak, in the current clinical practice concerning use of LC-MS in Vitamin D testing," stated Rao. "We

laboratorians recognize the precision of the LC-MS method, which requires a highly-trained and dedicated technician. It's very accurate and interference-free compared to immunoassays.

"However, as demonstrated in our laboratory's experience providing physicians with Vitamin D results generated by both methods, for the LC-MS assay to have clinical relevance, I believe LC-MS results must agree with the immunoassay," offered Rao. "Accomplishing such a correlation has been the unsolved challenge for our laboratory.

Explaining Bias Factor

"For example, from our 600-patient population, we did establish a bias factor for our home brew LC-MS assay relative to the Liaison CIA that we've used for years," he explained. "Next, we went to several client physicians and asked them, 'Should we establish a bias factor and represent both the LC-MS value and the immunoassay equivalence to you on the test report?'

"These physicians initially liked this idea," noted Rao. "So, we offered both LC-MS measured values and calculated immunoassay equivalent values in the patient report. This created confusion among some physicians as to what number for a Vitamin D result was appropriate upon which to base their clinical actions. In response to this, we removed the calculated value from the patient test reports."

Complications For Clinicians

This experience of the laboratory at the University of Massachusetts Medical Center demonstrates how the widening use of LC-MS assays for Vitamin 25(OH) D testing can bring complications to the clinical environment. For clinicians, unaware of the fact that the LC-MS methodology typically produces different (and often higher) numbers than the long-accepted immunoassay methodology, there is the potential for them to inappropriately evaluate the patient. In turn, that might mean the patient gets the wrong treatment for their true condition.

This same situation often causes physicians to question the credibility of the laboratory which reported the Vitamin D result. These doctors will contact the reporting laboratory and question the accuracy of the Vitamin D results it reported. This is often the case when a physician is using multiple labs because of managed care contracts.

Rao believes some resolution to this situation may come from a new development. "On July 14, the **National Institute of Standards and Technology** (NIST), in collaboration with the **National Institutes of Health's** Office of Dietary Supplements (NIH-ODS,) announced the development of a new reference sample for Vitamin D," stated Rao. "It is called NIST Standard Reference Material (SRM) 972–Vitamin D in Human Serum.

"This SRM will provide stable, well-defined levels of the analytes of interest," he explained. "It will serve as a reproducible point of comparison, of results across different methods and within the lab over time.

"NIH-ODS also announced an ODS-funded NIST quality assurance program for analysis of Vitamin D metabolites in human serum," concluded Rao. "NIST chemists will compile data and provide the laboratory with confidential feedback about its performance These are positive first steps towards standardization of Vitamin D testing."

As the experience of the laboratory at the University of Massachusetts Medical Center demonstrates, the widening use of LC-MS assays for Vitamin 25(OH) D testing has brought complications to the clinical environment. For clinicians, unaware of the fact that the LC-MS methodology typically produces different numbers than the long-accepted immunoassay methodology, there is the potential for them to inappropriately evaluate the patient. In turn, that might mean the patient gets the wrong treatment for their true condition. **TDR**

Contact L.V. Rao, Ph.D., at 774-443-7593 or Lokinendi.Rao@Umassmemorial.org.

Lab M&A Deals in June Show Market Direction

Buyers support labs offering unique tests for companion diagnostics and personalized medicine

CEO SUMMARY: Despite a dismal economy, the month of June spawned two interesting merger/acquistion transactions in the lab testing industry. In one case, a blood brother gobbled up a specialty diagnostics company. In another transaction, two cross-town neighbors in Kansas City merged to form an enhanced specialty diagnostics laboratory company. The common theme behind both transactions was motivation to acquire resources and technology in companion diagnostics and personalized medicine.

JUNE WAS AN ACTIVE MONTH for laboratory mergers and acquisitions. Two transactions occurred, spurred by the race to serve the nascent demand for companion diagnostics and tests that support personalized medicine.

First came the announcement on June 23 that **Laboratory Corporation of America** of Burlington, North Carolina, would acquire **Monogram Biosciences, Inc.**, of South San Francisco, California. In an all-cash deal, LabCorp will pay $106.7 million, or $4.55 per share.

Monogram sells a number of tests used in HIV testing and to determine which therapeutic drugs may be appropriate for an HIV-infected patient. It also has a HER/2 test for breast cancer.

The second transaction was a merger involving two laboratory companies located just 22 miles from each other. On June 30, **ViraCor Laboratories** of Lee's Summit, Missouri, announced its merger with **IBT Laboratories** of Lenexa, Kansas.

In the merger, ViraCor, a molecular diagnostic testing company specializing in infectious diseases, joined together with IBT, a clinical diagnostics and biomedical-research laboratory that specializes in immunology and allergy assays. The new ViraCor IBT company is a specialty diagnostics laboratory.

"This merger was driven by rapid changes in the lab testing marketplace," stated John Martin, President of the combined lab company. "Clients want more from their diagnostic laboratory providers in terms of state-of-the-art diagnostic testing and technology platforms. We thus saw the need to increase our menu of offerings to allow us to more effectively partner with healthcare providers in support of better case management and better ways to treat patients."

Sign Of A Larger Trend

"These two examples (ViraCor-IBT and LabCorp-Monogram) affirm a trend that has been going on internally with the big companies for some time," said Gregory J. Tsongalis, Ph.D., Director, Molecular Pathology and Co-Director, Pharmacogenomics Program, at the **Dartmouth Hitchcock Medical Center** in

Lebanon, New Hampshire. "That is, acquisition of smaller diagnostic companies with novel lab test technologies and expertise to help move things more quickly through the pipeline.

Matching R&D And Clinical

"In fact, the lab here at Dartmouth is an example of this trend" noted Tsongalis. "We formed our own translational research lab for R&D purposes. Not only did that result in significant savings for the clinical lab, but it has brought us many more academic collaborations than we could have accomplished with just the clinical laboratory.

"Based on our experience, this same thing is happening with the larger laboratory companies," he added. "Among these companies, the competition is fierce. Having a program to acquire and access unique diagnostic technology that can support companion diagnostics is becoming a critical success factor."

That's the same message coming out of the recently merged ViraCor IBT, which points out that it has a strong research and development infrastructure. This gives it broader scientific proficiency for physicians, hospitals, and researchers in immunology and infectious diseases. Together, Viracor and IBT can offer enhanced services to biopharmaceutical companies doing drug discovery and clinical-trial testing.

Want Three Lab Capabilities

"Physicians and hospitals want laboratory and diagnostic providers—and especially the specialized segments of our industry—to do more than simply provide lab test results," Martin explained. "They look for three capabilities. First, they want labs that will help them better serve their patients. Second, they want the state-of-the-art science and service. Third, they want labs that can grow with them. Essentially, clients tell us that they want their laboratory to be a long term partner as lab test technology advances in support of companion diagnostics and personalized medicine services.

"At ViraCor and IBT, we broadly define our target market as conditions affecting the immune system," he continued. "This market includes allergy, immunology, infectious disease, and the like—along with hospitals, physicians, and pharmaceutical clients developing therapeutics in this field. For these clients, the new ViraCor IBT company has an extremely comprehensive offering.

"In response to the evolution we see in the clinical and research marketplace, our business strategy is to marry diagnostic technology with a scalable business model," concluded Martin. "This keeps us relevant in the eyes of our clients, who value our broad test menu which is specialized to their needs."

Lab Mergers & Acquisitions

With two laboratory merger and acquisition deals in June, it can be considered a busy month, given an economy in recession. However, there is a more important insight from these two deals for pathologists and lab managers.

In both examples, motivation for the transaction was buyer interest in a laboratory that had specialty molecular expertise and the capability to service the emerging demand for companion diagnostic assays and testing in support of personalized medicine. Interesting confirmation of this market development came from Tsongalis, who reported on the success that resulted from the creation of the translational research lab at Dartmouth Hitchcock Medical Center.

Collectively, these developments demonstrate the importance for laboratories to have the right partners and access to advanced diagnostic technology. That's because clients of specialized lab testing seem to be raising the bar on their lab providers. TDR

Contact John Martin at 800-305-5198; Gregory Tsongalis, Ph.D., at 603-650-5498 or gregory.j.tsongalis@hitchcock.org.

New Flu Strain Expected In Upcoming Flu Season

Nation's public health laboratories continue influenza testing at relatively high volumes

CEO SUMMARY: Public health labs continue to monitor for new cases of the A/Novel H1N1 flu, while preparing for what may be a difficult flu season this fall. Having coped with a 10-fold increase in testing volume, public health labs are assessing the lessons learned from the April/May flu outbreak. At the Association of Public Health Laboratories, activities are underway to better coordinate the services of public health labs in different regions of the country, as well as to develop contingency plans to ensure ample supplies and reagents for any future outbreak.

PUBLIC ATTENTION TO INFLUENZA A/NOVEL H1N1 MAY BE RECEDING, but public health laboratories still see a relatively high volume of flu testing as efforts continue to identify and study this new influenza strain.

"People forget that in the United States, 36,000 people die every year of seasonal influenza," stated Rosemary Hume, Senior Advisor, Scientific Affairs, at the **Association of Public Health Laboratories** (APHL) in Silver Spring, Maryland. "Influenza is a serious disease whether it's seasonal or novel. Fortunately this novel virus has so far turned out to be probably no more serious than seasonal influenza—but this strain could change over the summer. That is why close surveillance of new flu cases continues."

The relative high volume of flu samples that continues to arrive in public health laboratories indicates that A/Novel H1N1 has not disappeared during the summer in the United States. That is one reason why public health officials believe that A/Novel H1N1 is likely to be present during the upcoming flu season, In turn, that has public health laboratories assessing the lessons learned during the initial outbreak of A/Novel H1N1, first identified in late April.

"APHL serves as the primary point of contact for the federal **Centers for Disease Control and Prevention** (CDC) to reach public health labs in the United States," noted Hume. "So we were among the first that the CDC alerted to the discovery of the new influenza strain. In turn, we distributed information to our members, conducted regular conference calls, and sent email alerts to communicate new findings from the CDC to the nation's network of public health labs.

CDC Experts

"This allowed us to bring the public health lab community together with CDC subject matter experts to discuss testing issues and to learn which states were seeing increasing demand for A/Novel H1N1 testing," Hume continued. "During that time, we also surveyed our members on how they were doing and what they needed.

"We learned, for example, that there were backlogs in testing and, in some locations, there were shortages of supplies and reagents," she added. "It was also quickly recognized that, given the flood of flu specimens for testing, there was an inadequate number of trained laboratory staff to meet that high demand for testing.

Shortage of Lab Staff

"Of all the limiting factors faced by public health laboratories, it was probably the shortage of staff at many facilities that limted or restricted their ability to respond in the most effective way," noted Hume.

"In fact, one important lesson learned from this outbreak is that surge capacity is limited across the laboratory sector—in large part because clinical labs and public health labs are struggling to find enough qualified people to work in labs," she observed. "There are workforce shortages in every sector of laboratory medicine. But public health labs have an acute staffing problem because of budget cuts in many states in recent years.

"That makes it important to have good strategies for triaging specimens, even as clinicians get good clinical guidance so they know which patients should be tested and which patients should not be tested," continued Hume. "There will always be a demand for testing by the worried well. So every lab needs to have adequate resources—such as a rapid tests and point of care tests—and know how to use them judiciously.

Ongoing Data Collection

"We continue collecting data about this outbreak and ongoing transmission of this flu strain," she stated. "Hardest hit by A/Novel H1N1 have been California, Illinois, Texas, and Wisconsin. But even in states that were not hit hard, there was a high demand for testing. In this way, this novel strain pandemic was quite similar to what we have seen in other outbreaks. Fortunately, we were prepared because every state could do influenza typing using the CDC's five-target assay. Any unsubtypable specimens were sent to the CDC for confirmatory testing.

"Following the identification of A/Novel H1N1 in late April, the response of public health labs was good, in part because we have been working with the CDC on pandemic planning since about 2003," Hume said. "Since then, important steps were taken to prepare for a novel flu outbreak or pandemic. The focus was largely on the avian flu. But we knew we could be surprised with any strain. Therefore, much of this extensive preparation paid off during this event.

"In 2003, the CDC developed the five-target assay, which is a PCR protocol for the detection and subtyping of seasonal influenza and the H5 avian flu," explained Hume. "It was just a test protocol; it wasn't a kit. That test was rolled out to all the public health labs. These labs were provided training on that assay, which, for several years, served as the foundation for enhanced surveillance of the potential introduction of the novel strain. Public health labs have had ongoing training in how this assay would be used."

Progress Since 2001

THE DARK REPORT points out that one important dimension to the public health laboratory response to the A/Novel H1N1 outbreak this spring has gone unreported by the major media. The effective response to this flu outbreak is a direct consequence of additional funding and resources that were made available to the CDC and public health agencies since 2001.

Increased funding over this decade was triggered by three events: in 2001, it was 9/11 and the anthrax attacks. In 2003, it was global concern about SARS and Avian flu. In 2009, public health laboratories were much better prepared to respond to influenza A/Novel H1N1 compared to 2003, when SARS first was detected. Also, in this latest flu pandemic, faster and more sensitive molecular testing technology made an important contribution to disease detection and epidemic control efforts. TDR

Contact Rosemary Hume at 240-485-2745 or rosemary.hume@aphl.org.

New Molecular Testing Technology Plays Essential Role in Outbreak of A/Novel H1N1 Flu

MOLECULAR DIAGNOSTIC TESTING TECHNOLOGY proved an effective tool for rapid testing and subtyping during the recent outbreak of A/Novel H1N1 influenza.

"It only took about 12 days for the Centers for Disease Prevention and Control (CDC) to develop a test specifically for this novel strain of A/H1N1," stated Rosemary Hume, Senior Advisor, Scientific Affairs, at the Association of Public Health Laboratories (APHL). "The CDC had it manufactured, packaged, quality-controlled, and out the door.

Flu Kits Shipped On May 1

"Those diagnostic test kits were shipped to public health laboratories on May 1," she continued. "Our public health laboratory members were using these new test kits and reporting results during the week of May 5. To accomplish that within two weeks of the outbreak is an outstanding achievement.

"At that time, when A/Novel H1N1 was first identified, in the United States there were 36 public health labs that had both the FDA-cleared flu tests and the training to use these tests," Hume said. "In fact, 43 states were completely ready—meaning their public health labs had been trained to use the diagnostic instruments before the outbreak. Thus was the result of a training program instituted last year on how to run the five-target assay on the **Applied BioSystems** 7500 Fast Dx. *(See TDR, June 8, 2009.)*

"Most public health laboratories in the United States had already installed the 7500 Fast Dx for use in research," she continued. "But these instruments hadn't yet been upgraded with the diagnostic capability. Thus, the right instrument was already in place, most lab staff had undergone previous training, and most were knowledgeable in using the FDA-cleared test. So the swine flu assay only needed to be added to the FDA-cleared five-target influenza assay.

Changed Out The Primers

"That shows the level of preparedness across the public health laboratories in this country," observed Hume. "CDC-developed flu kits shipped out on May 1 were based on the FDA-cleared seasonal influenza test, developed primarily to detect swine flu. These updated kits used the same procedure and ran on the same equipment. CDC changed out the primers and the probes for the novel new A/H1N1strain of swine flu.

"In recent years, we've seen about 20 cases of swine flu annually in the United States. But it's a different strain than A/Novel H1N1," she said. "The strain we normally see results from human contact with hogs. It is usually a self-limiting strain and does not transmit from human to human. That is why, in the early days of this outbreak, the first question was: Is this strain a novel strain?

Ongoing Data Collection

"Back in 2007, as the CDC rolled out its five-assay influenza test, it recognized the need to provide standardized reagents. To do that, it was necessary to develop an FDA-cleared influenza test," added Hume. "So the Association of Public Health Laboratories worked with CDC to do all of the validation studies. By October 2008, the CDC obtained clearance for the new five-target assay, which needs to be run on a PCR platform. The CDC used the 7500 Fast Dx.

"All this planning in recent years positioned public health laboratories to respond quite quickly to the emergence of the novel A/H1N1 influenza," concluded Hume.

Elevating Lab Testing At Policymaking Table

➤CDC engages Battelle Corporation to identify and publish laboratory medicine best practices

➤➤CEO SUMMARY: With the help of contributing clinical laboratories, the CDC has launched an ambitious effort to gather data, apply evidence review methods used in clinical studies, then identify and publish best practices in laboratory medicine. The goal is to advance the value of laboratory medicine. Some lab experts believe this effort may produce the type of credible information that helps lab testing move away from commodity-based pricing in favor of value-based reimbursement.

JUST AT THE MOMENT when Congress and the new administration is prepared to implement radical reforms to the nation's healthcare system, a credible effort to identify and publish evidence-based best clinical practices utilizing laboratory testing has launched.

If the goal of the lab industry is to educate healthcare policymakers about the incredible value of laboratory testing and move the discussion away from treating a lab test as a commodity, as if it was salt or lumber, then laboratory leaders across the country should take time to learn more about this new effort.

➤CDC Teams With Battelle

It is the Laboratory Medicine Best Practice Project. At the **Centers for Disease Control and Prevention** (CDC), the Division of Laboratory Services contracted with **Battelle Memorial Institute** to identify and publish evidence-based best practices in laboratory medicine. In particular, the project will focus on the pre-analytical and post-analytical stages, which starts when clinicians order laboratory tests and ends when they use the lab test results in patient care.

Battelle is recruiting laboratories to participate in this effort. In one public document, Battelle explains the project:

Systematic evidence review methods are standard practice in clinical medicine and public health, but are rarely applied to laboratory practices in the pre- and post-analytical phases of the total testing process.

In previous work, we adapted these methods to evaluate laboratory medicine practices. Because published evidence for laboratory practice effectiveness is limited, Battelle is developing a laboratory network to reach beyond the published literature. The network will identify and evaluate unpublished studies by laboratory partners that address specific quality improvement, cost, or patient safety issues, using the same rigorous criteria applied to published studies.

"A specific objective of this project is to identify, evaluate, and publish laboratory best practices that meet the standards of evidence-based medicine (EBM)," explained Paul Epner, who is Network Administrator for the Laboratory Medicine Best Practice Project. "This project came

about because, at this time, little published literature exists that supports laboratory medicine best practices throughout the total testing process, but especially in the pre- and post-analytical stages."

Pre- And Post-Analytical

Epner points out that a major objective of this effort is to shift attention away from the analytical step in laboratory testing—which tends to get lots of attention and resources by laboratory professionals. Instead, the project will concentrate upstream, from the point when a clinician decides to order tests and the lab collects the specimens; and downstream, as the laboratory reports the test results and the clinician determines which course of action is indicated for the patient. Published literature indicates that most errors affecting patient safety and outcomes occur in the pre- and post-analytical phases .

"Surveys show that most laboratory managers focus on factory-like measures of performance, such as cost per test, billables per FTE, in-lab cycle time (accessioning to result release), or employee safety and satisfaction," observed Epner. "Meanwhile, healthcare policy debates focus on clinical and economic outcomes and the factors that drive them.

Improve Outcomes

"A central theme of these debates is the performance of our healthcare system and the incentives necessary to improve outcomes and lower utilization of resources," he continued. "This debate has led to innovations such as pay-for-performance and evidence-based medicine (EBM). As a source of reform, EBM is intended to reduce variations in care left unexplained by clinical findings and to limit the adoption of new, more expensive and unproven technologies."

That is why the Laboratory Medicine Best Practice (LMBP) Project has the potential to be a strategic game changer for pathology and laboratory medicine. Many healthcare policymakers view laboratory medicine as a commodity. This perception is a result of the vacuum of evidence-based medicine studies that demonstrate how effective use of the right laboratory test—at the right time with results coming from a valid and reliable process—can significantly improve patient outcomes at minimal cost. Lacking such credible sources of information, many policy makers think of the laboratory as though it were a factory turning out numbers—instead of an essential member of the patient care team.

Sustainable Process

"Laboratory medicine and pathology need a sustainable process for generating evidence-based best practice recommendations in laboratory medicine to improve healthcare quality—and which also have credibility with healthcare policymakers," observed Epner. "As part of the LMBP project, the methodology for collecting and evaluating evidence was established and a pilot test of the process is underway. One early finding confirmed the lack of sufficient, high quality peer-reviewed literature to determine laboratory best practices.

"The CDC, through Battelle, is ready to help the laboratory profession expand the available evidence," added Epner. "This will be accomplished by using unpublished data from laboratories that is generated during their normal operations and from their quality improvement projects. Systematic review methods will be used to evaluate the findings and assemble evidence summaries as if they had come from published sources."

Laboratory managers and pathologists interested in advancing these aspects of laboratory medicine are invited to participate in the project. According to Epner, a lab's participation will require no extra effort, for an interesting reason.

"Participating labs need only submit data that they already collect!" said Epner. "This makes it easy for labs to participate. Sources can be existing data from retrospective observational studies, case stud-

ies, quality improvement projects, and FMEA studies, for example.

"Data will be de-identified with respect to patients and facilities, with only system demographic information being retained for evidence review," he continued. "Data submission will be accomplished through an online portal at the project's website *(www.futurelabmedicine.org)* or through completion of a data form based in Excel. Other than the time required to prepare and submit the data, no other meaningful costs or resources are required for a laboratory to participate.

"The Laboratory Medicine Best Practice Project is expected to advance knowledge in two direct ways," commented Epner. "One, based on study data and evidence review methods, effective best practices in laboratory medicine will be identified that have demonstrated desirable impacts on clinical outcomes. The nation's labs can then use these EBM findings to improve and advance the quality of the lab testing services provided by their laboratory.

"Two, the availability of these evidence-based laboratory best practices is expected to open more doors for pathologists and laboratory professionals to participate in high quality clinical research and contribute to the improvement of healthcare delivery in the United States," he said.

➤Quality of Lab Testing

As a consequence of the publication of evidence-based laboratory medicine best practices, Epner and his colleagues also see strategic benefit. "The accumulation of these peer-reviewed, credible findings about the value of laboratory medicine is expected to open more doors for laboratory professionals," he predicted. "It may even reserve a welcome place at the healthcare policymaking table for laboratory medicine."

THE DARK REPORT observes that this is a unique opportunity for the laboratory medicine profession. Not only is the CDC putting its imprimatur behind this laboratory best practices project, but it is also providing the resources (Battelle Corporation) and the funding! Laboratory administrators and pathologists interested in shifting laboratory medicine away from its "commodity" status and over to an "added value" clinical asset should consider participating in this project TDR

Contact Paul Epner at 847-508-2810 or PEpner@ChicagoBooth.edu.

How Labs Can Participate To Identify Best Practices

TO ENCOURAGE WIDE PARTICIPATION by clinical laboratories across the country, the Laboratory Medicine Best Practice Project made it simple to volunteer and simple to submit data.

"Labs can register to become part of the Laboratory Best Practice Network by visiting *www.futurelabmedicine.org* and completing the registration information," stated Paul Epner, who is Network Administrator for the Laboratory Medicine Best Practice Project.

"Participating labs are asked to submit data and information that they already collect from normal operations and from their quality improvement projects," continued Epner. "For this reason, participation requires no additional measurement or data collection by the participating laboratory.

"Data submitted should be patient-deidentified. Labs have the option to be individually identified or remain anonymous in published findings of lab best practices," he added.

The first phase of this project will evaluate and identify best practices in three areas:

- Reducing patient specimen identification errors
- Timely, accurate communication of critical laboratory test results
- Preventing blood culture contamination

For more information: http://www.futurelabmedicine.org

INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

Larry Siedlick resigned as CEO of **Sunrise Medical Laboratories** in Hauppauge, New York, effective June 30. It was 2007 when Siedlick and partner Pat Lanza sold their interest in the laboratory they founded back in 1972 to **Sonic Healthcare, Ltd.** Siedlick tells THE DARK REPORT that he will be developing two laboratory service companies. One is **ARx, Inc.**, which offers contract billing services and a business intelligence dashboard for clinical labs. The other is **Laboratory Management Services**, a "healthcare integration services company that unites leading health plans and clinical laboratories."

PRISON TESTING IS GOOD NICHE BUSINESS AT BIO-REFERENCE LABS

It pays to develop niche markets in the laboratory marketplace. On July 7, *Investor's Business Digest* profiled **Bio-Reference Laboratories, Inc.** (BRLI), and reported that the Elmwood Park, New Jersey, laboratory now holds a 60% share of prison testing in the United States. According to *Investor's Business Digest,* BRLI holds contracts with 11 state prison systems, generating about 10% of the company's annual revenue.

TRANSITIONS

• **ARUP Laboratories, Inc.** of Salt Lake City, Utah, announced that Edward R. Ashwood, M.D., would be moving to the position of President and CEO. Sherrie L. Perkins, M.D., Ph.D., was named as Chief Medical Officer and Director of Laboratories. These changes are in response to the retirement of ARUP Laboratories' founder and CEO Carl R. Kjeldsberg, M.D., that was announced last month.

• At **DCL Medical Laboratories** (DCL) in Indianapolis, Indiana, Jay Tyler is the new CEO, following the departure of former CEO Michael Hanbury, Ph.D., in May.

• Anne Daley has joined **Chi Solutions, Inc.** as a Senior Consultant. She was formerly with **Ascendium Healthcare Consulting** and earlier held management positions at **Sonora Laboratory Services** in Phoenix, Arizona.

• In Wayne, Pennsylvania, the **Clinical Laboratory Management Association** (CLMA) has engaged Wendell O'Neal, Ph.D., as interim CEO. O'Neal earlier served as Vice President of **Alliance Laboratory Services** in Cincinnati, Ohio, and has been active in laboratory consulting in recent years.

DARK Daily
Clinical Laboratory and Pathology News/Trends

DARK DAILY UPDATE

Have you caught the latest e-briefings from DARK Daily? If so, then you'd know about...

...the new study in the *New England Journal of Medicine* that estimates it will cost medical schools $1.6 billion per year to comply with the recommended reduction in the working hours and workloads of residents.

You can get the free DARK Daily e-briefings by signing up at www.darkdaily.com.

That's all the insider intelligence for this report. Look for the next briefing on Monday, August 10, 2009.

Now in its third year!

PREVIEW #2

Lab Quality Confab

on Quality Management in Diagnostic Medicine

September 29-30, 2009 • Hilton Hotel• Atlanta Georgia

Patrick Horine of DNV Healthcare on:

New Choice for Hospital/Health Systems: Earn Accreditation for Medicare & ISO 9001 at Same Time!

Move over Joint Commission! Hospitals and health systems have a new choice for Medicare accreditation—that also allows them to earn ISO 9001 accreditation at the same time. Learn why progressive hospitals/health systems are utilizing DNV Healthcare to achieve this accreditation double play. Understand how hospitals and labs are benefiting from use of ISO 9001 methods in their organization. Join us for this special, first-ever presentation at Lab Quality Confab!

For program details and to register:
visit www.labqualityconfab.com

UPCOMING...

- ***Our Editor Gives Blood For the Cause! How 8 Labs Reported His Vitamin D Results.***
- ***Another New Laboratory Company Targets Breast Cancer Market with Proprietary Assay.***
- ***Lean Triggers 50% Gains in Histology Lab Performance at Henry Ford Health System.***

For more information, visit:

www.darkreport.com

Sign Up for our FREE New Service!

Delivered directly to your desktop,
DARK Daily is news, analysis, and more.

Visit www.darkdaily.com

DARK Daily
Clinical Laboratory and Pathology News/Trends