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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

New Cycle Begins for Lab and Pathology Acquisitions

THERE'S A NEW TRANSITION JUST GETTING STARTED in the laboratory testing industry. For the past two decades, laboratory acquisition activity has primarly centered around independent clinical laboratories—often owned by local pathologists. This was true in both the size of the transactions and in the volume of transactions. Our stories on pages 3-9 describe these processes.

That is about to change. From 2010 onward, laboratory acquisition activity is likely to center around two different segments of the laboratory testing industry. One segment involves the laboratory outreach businesses owned and operated by hospitals and health systems. The second segment is comprised of the regional and local anatomic pathology laboratories and group practices owned by pathologists. For both segments, a new cycle of acquisition activity is now beginning.

In segment one, in the 14 months since January 2009, four significant acquisitions of hospital/health system-owned lab outreach businesses have taken place. Plus, there is the investment by **Catholic Health Initiatives** (CHI) in **Pathology Associates Medical Laboratories** (PAML) that happened in November 2009.

Collectively, these laboratory acquisitions and investments demonstrate that hospitals and health systems are waking up to the substantial value that is created from a profitable laboratory outreach program. It is reasonable to expect that—as hospital CEOs learn about these acquisitions and the prices realized by the sellers—more hospitals and more health systems will be willing to entertain the sale of their laboratory outreach businesses.

For segment two involving anatomic pathology laboratories, the simple fact that will drive laboratory acquisitions is the pending retirements of baby boomer pathologists who are partners in these laboratories and pathology group practices. That motive played a role in most of the pathology laboratory acquisitions announced during the past 14 months. *(See table on page 5.)*

I believe the longer-term impact of these developments will be the further consolidation of both segments of the laboratory testing industry. Deal-by-deal, hospital laboratory outreach business will be sold and resold into the hands of the nation's largest lab operators. A similar process will unfold in anatomic pathology. It will take some time to consolidate the 3,300 independent pathology practices that exist today, but that cycle of change is now under way. TDR

Pace of Lab Acquisitions Increased during 2009

Lab buyers show strong interest in acquiring both clinical labs and anatomic pathology groups

CEO SUMMARY: After two years of relatively slow sales of clinical labs, there is pent up demand for lab acquisitions and a declining supply of independent labs available for sale. That's the assessment of one expert on laboratory mergers and acquisitions, who predicts that the accelerating pace of clinical lab and anatomic pathology practice acquisitions seen in the second half of 2009 is likely to carry on well into 2010. Professional investors continue to look for opportunities to buy into the laboratory testing market.

DESPITE THE MOST SEVERE ECONOMIC RECESSION in almost 30 years, 2009 turned out to be an active year for laboratory mergers and acquisitions (M&A). There was a steady parade of laboratory acquisitions announced throughout 2009.

"This strong M&A activity in the second half of 2009 represented a marked change from the first half of 2009 and the second half of 2008," observed Chris Jahnle. "By the end of 2008, laboratory M&A was in the doldrums, due to the economic recession. Many sellers and buyers were on the sidelines waiting to see what would happen with the economy."

Jahnle is Managing Director of **Haverford Healthcare Advisors**, in Paoli, Pennsylvania. Jahnle has 25 years of experience in the valuation of clinical laboratories and pathology group practices, along with extensive experience in laboratory mergers and acquisitions (M&A).

"For a long period of time—because of the recession—many active sellers took their labs off the market, giving lab buyers fewer choices," said Jahnle. "This factor contributed to the slower pace of laboratory mergers & acquisitions during late 2008 and early 2009, compared to late 2009. Despite the high interest of lab sellers and lab buyers, during 2008, both sides were waiting out the recession. The slow pace of lab acquisitions continued through the summer of 2009.

"By count of actual lab M&A transactions announced since mid-2009, activity began to accelerate and has carried over into the start of 2010," stated Jahnle. "This is due to two factors.

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"One factor is the brightening economic picture," he explained. "After two years of recession, key signs during 2009 indicated that the economy was in the early stages of recovery. For sellers, that pointed to stronger prices for their laboratory. For buyers, increased access to capital and improvement in the valuation of publicly traded laboratory companies fueled higher proposed valuations which, in turn, triggered more completed transactions.

Lab Acquisition Activity

"The second factor is that some laboratory acquisition deals that had commenced perhaps 18 to 24 months ago were finally completed," added Jahnle. "Watching these deals close in mid-2009 encouraged other lab sellers to put their companies up for sale.

"The resulting increase in the number of laboratories offered for sale during the last half of 2009 gave impatient buyers the opportunity to bid for some high-quality clinical labs and pathology group practices," he noted. "That pent up demand for labs is what fueled the number of M&A deals that closed during 2009 and even made the first weeks of 2010 busy with acquisition announcements.

"Another difference about the laboratory M&A market during 2009 is that new buyers crowded in to bid against the two national laboratories," stated Jahnle. "Of the 24 lab acquisitions identified by Haverford Healthcare Advisors during 2009 and into early 2010, only four were purchased by **Laboratory Corporation of America** and **Quest Diagnostics Incorporated**.

New Buyers Bid For Labs

The two national labs regularly find themselves bidding against other strong buyers," he continued. "For example, such well-capitalized companies as **Sonic Healthcare, Ltd.**, and **Bio-Reference Laboratories, Inc.**, can bid for almost any laboratory company that is available for acquisition.

"Private equity firms are also motivated buyers and are often willing to outbid the nation's biggest lab companies," noted Jahnle. "In fact, 2009 ended with **Welsh, Carson, Anderson, and Stowe** acquiring **Spectrum Laboratory Network** of Greensboro, North Carolina. Within weeks of that sale, Welsh Carson then negotiated a deal with **Carilion Clinic** to merge **Carilion Labs** of Roanoke, Virginia, with Spectrum Lab Network.

"It should be noted that the combination of Spectrum Lab Network and Carilion Labs creates one of the biggest clinical laboratory companies in the United States," he added. "This shows how private equity companies can reshape the clinical laboratory marketplace. It is likely that Welsh Carson will pursue other laboratory acquisitions as a way to expand its business."

Jahnle had interesting observations about the growing activity in the anatomic pathology sector of the laboratory testing industry. "Wall Street investors believe there is a bright future for anatomic pathology," stated Jahnle. "They understand how the demographics of aging will drive up the incidence of cancer.

Promising Future For Labs

"They also recognize how genetic and molecular technologies are giving pathologists valuable new tools to diagnose disease and guide therapeutic decisions," he commented. "Together, both trends point to a robust and profitable future for laboratory testing. Professional investors want to buy a place in this market so they can profit from the ever-growing demand for anatomic pathology services."

"However, until 2009, most of the merger and acquisition activity in the anatomic pathology sector involved specialty pathology companies organized to compete nationally for case referrals," he observed. "Thus, it is notable that 2009 saw several transactions where larger, regional pathology group practices sold all or some of their business to private equity investors.

Clinical Laboratory Transactions Summary for 2009/2010 YTD

Transactions for 2009:

Date	Buyer	Seller	Purchase Price*	Revenue of Target
Jan-09	Gamma-Dynacare	Central Medical Laboratories	ND	ND
Jan-09	American Pathology Partners	UniPath, LLC	ND	ND
Jan-09	Surepath	Annapath Inc.	ND	ND
Mar-09	American Pathology Partners	Eastern Carolina Pathology	ND	ND
April-09	Water Street Healthcare Partners	ConVerge Diagnostic Services	ND	ND
May-09	Quest Diagnostics	OralDNA Labs	ND	ND
May-09	Management Team	Parkway Clinical Labs	ND	ND
Jun-09	Sonic Healthcare	Axiom Laboratories	$7,000,000	$5,000,000
Jul-09	Laboratory Corporation of America	Monogram Biosciences	$155,000,000	$62,000,000
Jul-10	Adeona Pharmaceuticals	HartLab LLC	$300,000	$150,000
Jul-09	Viracor	IBT Laboratories	ND	$35MM-$40MM
Sep-09	Quest Diagnostics	Caritas Medical Labs	ND	ND
Sep-09	Sonic Healthcare	Piedmont Medical Labs	$15,500,000	$11,000,000
Sep-09	ABS Capital	Pathology, Inc.	ND	ND
Nov-09	Aurora Diagnostics, LLC	South Texas Dermatopathology Lab	ND	ND
Nov-09	Bostwick Labs	Commonwealth Biotechnologies, Inc.	$1,100,000	$8,000,000
Dec-09	Aurora Diagnostics, LLC	Pinkus Dermatopathology Lab	ND	ND
Dec-09	Aurora Diagnostics, LLC	Bernhardt Laboratories	ND	ND
Dec-09	Welsh Carson Anderson & Stowe	Triad Lab Alliance, dba Spectrum Lab Network	ND	ND
Dec-09	Laboratory Corporation of America	Centrex Clinical Laboratories	ND	ND
Dec-09	Sonic Healthcare	East Side Clinical Laboratory	ND	ND

Transactions for 2010 YTD:

Jan-10	Primus Capital	PathGroup, Inc.	$100,000,000	ND
Jan-10	Triad, dba Spectrum Lab Network	Carilion Labs	ND	ND
Jan-10	Predictive BioScience	OncoDiagnostic Laboratory	ND	$10,000,000

* In millions • ND is "not disclosed • NA is "not available"

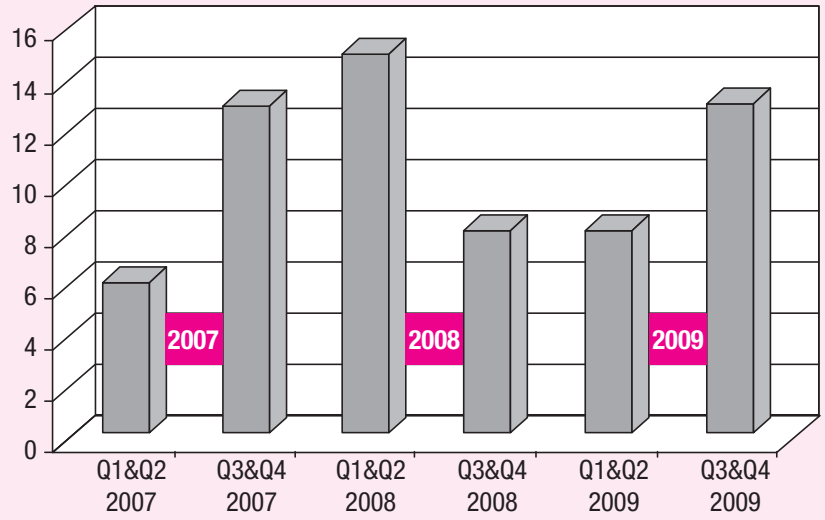
(Prepared by Haverford Healthcare Advisors)

"This was true in January 2009 when **UniPath, LLC**, of Denver, Colorado, sold certain assets to **American Pathology Partners** (APP) of Brentwood, Tennessee," said Jahnle. "Late in 2009, two other regional pathology powerhouse groups sold interests in their company to private equity investors.

"**Pathology, Inc.**, of Torrance, California (with 17 pathologists), sold ownership to a group that included **ABS Capital** and **ORIX Venture Finance LLC**, in September 2009," he noted. "In January 2010, **PathGroup, Inc.**, (with 50 pathologists) of Brentwood, Tennessee sold a minority interest to **Primus Capital Funds** and **Brentwood Capital Partners LP**. Including the senior debt that was part of the transaction, PathGroup generated $100 million from this transaction.

"Another sector of the laboratory testing market that saw increased action during 2009 involved hospital and health system-owned laboratory testing programs," continued Jahnle. "In at least five separate transactions, a hospital or health system sold the outreach laboratory testing business it had owned and operated, in some cases, for several decades.

Tracking Lab M&A Deals in Recent Years



This chart shows how laboratory M&A activity fluctuated during six month periods in 2007, 2008, and 2009. As the recession kicked in during early 2008, the number of lab M&A deals announced fell significantly during the second half of 2008 and the first six months of 2009. During the second half of 2009, the number of mergers and acquisitions climbed back close to former levels.

"I think this is a significant development," he noted. "It shows that hospitals and health systems are beginning to recognize that a successful laboratory outreach program can not only generate worthwhile operating margins, but can deliver significant capital value.

"For example, by selling **Centrex Clinical Laboratories** to LabCorp, **Faxton-St. Luke's Healthcare** received several tens of millions of dollars," explained Jahnle. "The health system CEO told the press that all the proceeds of the Centrex sale would be invested and go untouched so as to increase the health system's capital reserves.

Expect More Lab M&A

"Assuming that the economy continues to grow out of the recession, it is reasonable to expect that a steady flow of laboratory acquisitions will take place," declared Jahnle. "The fundamentals are in place to support an increased level of M&A activity throughout 2010."

Clinical laboratory and anatomic pathology lab mergers and acquisitions will be the subject of a special extended session at the *Executive War College on Laboratory and Pathology Management*, scheduled for April 27-28, 2010, at the Sheraton Hotel in New Orleans. At this session, Chris Jahnle will review completed acquisitions during 2009 and 2010, along with an assessment of laboratory valuations, deal terms, and important factors in the M&A market.

Lab owners and lab buyers interested in current developments in the laboratory M&A market should plan to participate in this popular, third annual "state of the lab M&A market" program. TDR

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Predict 2010 To Be Busy For Lab Owners & Buyers

Capital gains tax rates may rise next year and that may motivate laboratory sellers to do deals soon

CEO SUMMARY: Along with a recovering economy, the possibility of an increase in the capital gains tax rate for 2011 may encourage owners of clinical labs and anatomic pathology companies to sell their businesses during 2010. That could make 2010 a busy year for laboratory mergers and acquisitions, particularly if valuations for laboratory companies hold or increase from current levels. A growing number of credible buyers is another reason why laboratory sellers are likely to make 2010 a busy year for laboratory M&A.

FOR OWNERS OF CLINICAL LABORATORIES AND PATHOLOGY PRACTICES, 2010 shapes up be a very good year for them to put their laboratory up for sale. That may be true for at least two reasons.

"First, there is pent-up demand after two years of relatively slow sales," stated Christopher Jahnle, Managing Director of **Haverford Healthcare Advisors**, in Paoli, Pennsylvania. "As indicated by the number of lab acquisitions completed in recent months, there is an active group of qualified buyers looking for the opportunity to buy laboratories.

"Second, the capital gains tax rate may rise next year as the Bush-era tax cuts of 2001 expire at the end of 2010," continued Jahnle. "This is important, because if Congress allows the capital gains rate to increase in 2011, that would motivate laboratory sellers to close the sale of their lab during 2010 so that they would avoid paying increased taxes.

"We could also say that a third reason exists that encourages a higher rate of laboratory acquisition activity during 2010," he said. "It is an uncontested fact that today is a laboratory seller's market. That is because we see numerous buyers pursue a steadily-dwindling supply of independent laboratory companies. Thus, anytime a quality laboratory comes to market, it is guaranteed that numerous credible buyers will be interested in making an offer to buy that laboratory company.

Heightened Investor Interest

"This has always been true for the clinical laboratory side of the business," added Jahnle. "The new development we saw in the second half of 2009 is heightened investor interest in anatomic pathology laboratories.

"This bodes well for pathologists who are partners in anatomic pathology laboratories," he noted. "With more potential buyers in the mix, it means now is an interesting time for owners to consider a possible sale. Many signs point to more acquisition activity during the next six months.

"I suspect that, along with a recovering economy and the recent increase in the number of announced laboratory acquisi-

tions, laboratory owners will be motivated to shop their laboratories for sale due to the possible coming increase in tax rates.

"Let me explain," Jahnle said. "Lab sellers should consider that capital gains tax rates are scheduled to increase as of January 1, 2011. Thus, if their laboratory sales transaction can be structured so that their gain is characterized as a capital gain, sellers would be wise to complete a transaction in 2010 rather than 2011 and beyond.

"What triggers this change is the expiration of the Bush-era tax cuts, which reduced the capital gains tax rate from 20% down to 15% in 2001," he commented. "If Congress does nothing, then those tax cuts expire and, on January 1, 2011, the capital gains rate reverts back to 20%.

"...the high values of lab businesses seen in late 2007 and early 2008 were closely linked to the stock market valuations at the time."

"A smart seller can do the math," explained Jahnle. "A laboratory owner can look at that 5% tax increase and calculate how much he or she would need to grow the business to be at the same place as he or she would be if the sale went through this year as opposed to next year. The answer is that the growth would need to be substantial, and certainly greater than 5% to overcome an increase in taxes of 5%."

Valuations of laboratory businesses will play a factor in the laboratory M&A market during 2010. It is known that a number of laboratory sellers pulled their businesses off the market during 2008 and 2009 as they saw the prices paid for laboratories trail downward.

"In general, we currently see valuations that are lower than they were in the latter part of 2007 and the beginning of 2008," observed Jahnle. "However, the drop in prices was not much and I believe valuations have stabilized.

"Keep in mind that, even as some sellers took their lab businesses off the market because valuations were down, buyers for these same lab companies would have moved forward with a postponed transaction despite the slower acquisition market—if the seller would have taken a lower price. That is a reminder of the strong demand for laboratories.

Follows Stock Market Trends

"Laboratory valuations track the general economy and how the stock market values public laboratory companies," he stated. "For example, the high values of lab businesses seen in late 2007 and early 2008 were closely linked to the stock market valuations at the time.

"Typically, the prices at which shares of public lab companies like **Quest Diagnostics Incorporated** and **Laboratory Corporation of America** trade tend to be what influences the valuation of privately-owned clinical laboratories and anatomic pathology companies," noted Jahnle.

"To illustrate, take the price-to-revenue multiples paid for completed laboratory acquisitions," he explained. "Compare these to the revenue multiples at which the stock of public lab companies trades. There is a very close correlation. The ups and downs in the stock market are mirrored in the valuations paid to laboratories acquired in the same time period.

Tracking Valuation Trends

"For laboratory owners, a good valuation bellwether is the collective prices for stocks of publicly-traded lab companies," added Jahnle. "In a sense, you could say that 'as goes the share prices of Quest Diagnostics and LabCorp, so goes the broader trend line for the valuations of labs acquired during that time.'

"This valuation relationship for clinical labs and anatomic pathology companies has been true over the past two decades," he said. "It continues to be true today.

Valuation Follows Market

"A recent example demonstrates this principle," continued Jahnle. "Earlier this month, **Sonic Healthcare, Ltd.**, of Sydney, Australia, said it would acquire 100% of **Medhold NV**, a clinical pathology laboratory in Antwerp, Belgium, for $316 million. Sonic said that the price paid represented a multiple of 8.4 times earnings before interest, taxes, and depreciation (EBITDA).

"For Medhold, a valuation of 8.4 times earnings is just about the same multiple that the current share price for Quest Diagnostics represents," he observed. "Thus, the stock market's valuation multiple for Quest's EBITDA is within the same range as the price paid for Medhold NV. Therefore, the price paid by Sonic Healthcare is consistent with this trend."

Although cautious about predicting what lies ahead for laboratory mergers and acquisitions during 2010, Jahnle was willing to share some insights. He emphasized that there are at least four buyers with the financial capability to do almost any size deal.

"On the anatomic pathology side, there are a number of acquirers that were active in the final months of 2010..."

"Of course, LabCorp continues to be bid strongly for laboratory acquisitions as they come to market," offered Jahnle. "Similarly, Quest Diagnostics continues to seriously evaluate the laboratory companies which come to market.

"Sonic Healthcare has been one of the more regular acquirers in recent years," he noted. "I expect Sonic will continue to use lab acquisitions to expand its presence in the United States.

"The surprise player for 2010 is the return of **Welsh, Carson, Anderson, and Stowe** to the laboratory business," explained Jahnle. "In just a few weeks, Welsh Carson snapped up **Spectrum Laboratory Network** and then merged it with **Carilion Labs**. By combining these two laboratory companies, Welsh Carson now owns one of the nation's largest clinical laboratory businesses. Plus, it has the financial resources to pursue other large laboratory acquisitions.

Anatomic Pathology Labs

"On the anatomic pathology side, there are a number of acquirers that were active in the final months of 2010," he stated. "Two large pathology groups did deals with private equity investors. **American Pathology Partners** and **Aurora Diagnostics, Inc.**, continue to actively pursue acquisitions of anatomic pathology laboratories."

THE DARK REPORT observes that another factor likely to fuel an active year for laboratory mergers and acquisitions is the looming retirement of pathologists of the baby boomer generation. Anatomic pathology group practices will need a source of capital to cash out retiring partners. During 2010, the oldest baby boomer pathologists turn 64 years old. This demographic trend is likely to play a significant role in anatomic pathology mergers and acquisitions going forward.

In turn, a growing number of private pathology groups that accept investment capital from professional investors will become a new force for changing the competitive dynamics in the anatomic pathology marketplace. For these reasons, 2010 may turn out to be a year of significant change for the anatomic pathology profession. **TDR**

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Research Pathologists Use Next Generation Methods

Multispectral Tests Use "Smart" Systems To Analyze Tissue

➤➤CEO Summary: Pathologists at the Hospital of the University of Pennsylvania are using a new system that combines image analysis software and algorithms to evaluate images containing numerous stains and biomarkers. Pathologists teach the system to identify tumor cells and distinguish them from non-tumor cells. Now used for research purposes, this sophisticated digital pathology system is designed to do much of the manual activity required of a pathologist when assessing an image while producing highly accurate quantitative data.

EVEN AS WHOLE SLIDE SCANNING and digital pathology systems take root in the anatomic pathology profession, more technology surprises lie ahead. In research settings, smart software is already being used to analyze digital pathology images.

These systems combine automated image processing with analytical software that "learns" with each pathology image processed. One such system is "inForm", developed by **Cambridge Research & Instrumentation, Inc.** (CRi), of Cambridge, Massachusetts.

An early customer of CRi's technology now using the inForm system for research is the Pathology Department at the **University of Pennsylvania** in Philadelphia, Pennsylvania. Pathologists there are developing ways to evaluate pathology specimens using multiplex assays that incorporate numerous stains and biomarkers. Because so many different biomarkers are used, the analysis is quite complex.

This complexity goes beyond the capability of the human eye. What makes it possible to evaluate these pathology images is a combination of computer software and algorithms. Essentially, the computer uses its "smarts" to sort through the combination of stains and biomarkers to present the pathologist with its analysis of the cells, along with a precise mathematical score for selected variables.

"It is important to understand that, although the inForm software and Vectra multispectral imaging hardware 'automates' the analysis of these images, it is the pathologist user who directs the advanced features of the system to teach it what to recognize," stated Michael D. Feldman, M.D., Ph.D., Associate Professor of Pathology and Laboratory Medicine at the **Hospital of the University of Pennsylvania** (HUP) and a CRi collaborator.

"There is rapid progress in the field of digital pathology and pathologists should understand that our current work with these intelligent algorithms and a system like inForm adds one more dimension," noted Feldman. "These algorithms allow us to maximize the utility of hardware devices. For that reason, pathologists should expect to see a variety of different imaging algorithms enter the clinical market in the near future.

➤Seeking an Imaging Platform

"The Pathology Department at UPenn got involved with CRi because we wanted a technology platform capable of handling advanced imaging," he continued. "Specifically, our goal was to put down multiple protein marker antibodies onto tissues in a way that would allow us to identify their location in the tissue.

"For example, were they in a tumor, or a lymphocyte, or a blood vessel?" asked Feldman. "Once identified, we wanted a way to quantitatively and cytometrically analyze the information. That would allow us to see how these markers associate in such locations as the nucleus of a tumor cell, in the cytoplasm, or in the membrane.

"This technology goes beyond standard whole slide imaging," he said. "We realized from our clinical trials work that we needed a different analytic platform. We wanted what we call 'multispectral capability.'

"There was a host of specific biologic questions we couldn't answer with standard whole slide imaging," commented Feldman. "That led us to work with CRi. With CRi, we obtained a small business grant from the **National Institutes for Health** (SBIR) to develop and use this technology.

➤Cytometric Analysis

"We are also developing our own software in collaboration with Dr. Badri Roysam's lab at **Rensaleer Polytechnic Institute** to do certain types of cytometric analysis. Independent of our cytometric software, CRi is developing its own cytometric platform," he noted.

"Not only does this technology go beyond whole slide imaging, but it is down-

stream from computer-aided diagnosis as well," Feldman continued. "We work with tissues for which pathologists have already made the diagnosis of cancer.

"When I have a stained area in a field of view, I can tell the system to find the cancer region and the non-cancer region," he explained. "That allows me to then associate one or more stains with individual cells, along with their subcellular regions.

Quantitative Analysis

"If we know there is cancer on the slide or in the field of view, we can ask the inForm software to map every area where cancer exists," commented Feldman. "Next, the software will give me a quantitative analysis within those areas.

"What makes this a notable development is that the robot and software are doing the time-consuming manual part of the pathologist's work," he continued. "By doing this work for the pathologist, it extends his or her ability to diagnose more cases, thus boosting productivity.

"Think of it like this. No longer will a pathologist sit there and circle the areas which show the tumor regions. The system and the algorithms will do that for the pathologist with a very high level of confidence," said Feldman.

"When presented with this information by the system, the pathologist then applies his or her own domain knowledge," he explained. "The pathologist next views the work of the software and acknowledges that it correctly identified the areas of interest.

"This is the beauty of automated image processing and computer-assisted diagnosis," stated Feldman. "The software does automatically what would be time-consuming manual work for the pathologists, then presents the data for the pathologist to validate, verify, and interpret.

"This is how the system reduces manual steps that are time intensive," he added. "Once a pathologist adapts to this process, it speeds the analysis time for each image.

"Here's an example of how it works in our lab," said Feldman. "We're doing a clinical trial with the **Eastern Cooperative Oncology Group**. In this trial, we must assess how patients respond to different therapeutics. We have approximately 150,000 fields of view to evaluate.

"Imagine the time required for pathologists to properly analyze 150,000 views of information in the traditional manner, with a glass slide and a microscope," he observed. "There are not enough pathologists here at UPenn to handle all those images.

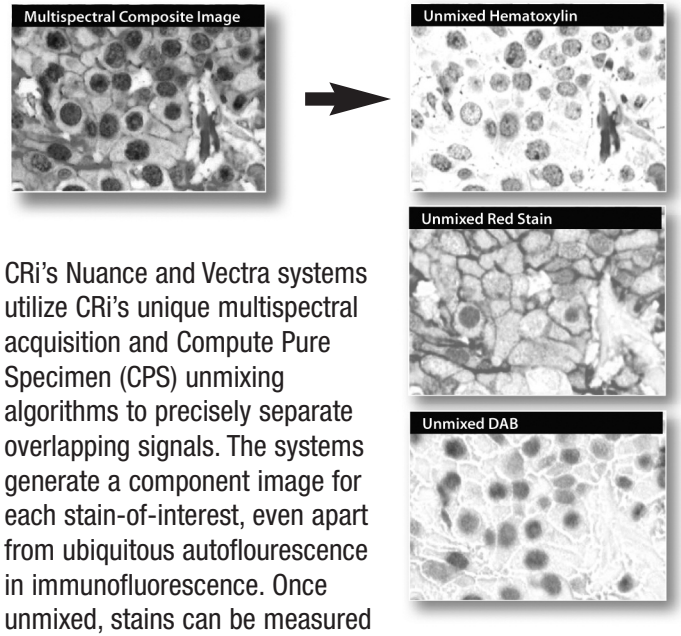
"For this clinical trial, we train the inForm system to evaluate the biomarkers and targets with a very high confidence," said Feldman. "This project, with its 150,000 images, would be nearly impossible to do manually. However, suddenly we can do this because of the automated functions and the machine learning algorithms within inForm. Moreover, as a pathologist using this system, it becomes a multiplier of my knowledge.

"This next-generation technology positions anatomic pathology for a huge breakthrough," he predicted. "The diagnostic state of the art today is working with one stain at a time," Feldman commented. "That's all we can do. But tomorrow, we will ask more complex questions that can't be answered with one stain at a time. Tomorrow the gold standard in pathology will involve working with two, three, and four stains at a time.

"Flow cytometry provides a parallel example," he continued. "Back in the

Software and Sophisticated Algorithms Used to Analyze Tissue Image That Is Comprised of Multiple Stains and Multiple Biomarkers

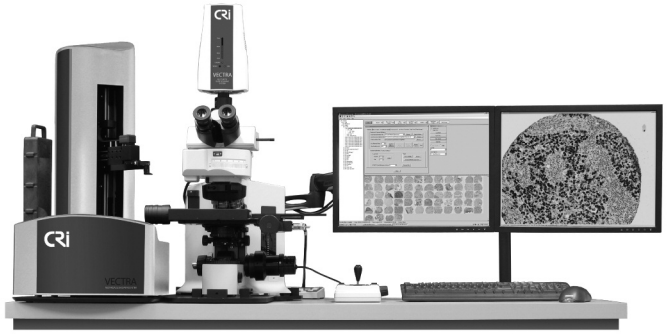
Spectral Unmixing of Overlapping Stains:



CRi's Nuance and Vectra systems utilize CRi's unique multispectral acquisition and Compute Pure Specimen (CPS) unmixing algorithms to precisely separate overlapping signals. The systems generate a component image for each stain-of-interest, even apart from ubiquitous autoflourescence in immunofluorescence. Once unmixed, stains can be measured accurately.

Nuance™ Multispectral Imaging System

Vectra™ Intelligent Analysis System



Pathologists at the University of Pennsylvania School of Medicine are using next-generation digital pathology systems to evaluate tissue images that contain multiple stains and multiple biomarkers. Above is shown a representation of a system that is capable of unmixing the different stains. The Nuance and the Vectra systems are part of CRi, Inc.'s suite of products designed to support advanced analysis of pathology images.

Increased Specificity Demonstrates Need for Pathology Labs to Eliminate Variation in Specimen Handling and Processing

"ELIMINATING VARIATION IN LABORATORIES is an important issue for the field of pathology," observed Michael D. Feldman, M.D., Ph.D., Associate Professor of Pathology and Laboratory Medicine at the Hospital of the University of Pennsylvania in Philadelphia. "It is time for our profession to pay increased attention to our analytes and develop better standards.

"There has been progress in addressing variability across laboratories," he added. "However, in surgical pathology, we need to start the process of standardizing how tissue is handled, processed, and manipulated.

Standardization Is Needed

"It will take some time to accomplish this, but standardization has to happen. Our entire industry needs to pay attention to this goal," said Feldman. "In addition to these standards, the pathology profession needs computer systems to help achieve this standardization. Today no lab information system exists that can capture all the data and all the fields required to provide confidence that the analyte to be evaluated is well-controlled.

"When asked, many pathologists respond by saying it is a daunting challenge to seek such standardization," recalled Feldman. "They say it's not likely that the profession will ever achieve standardization.

"On other hand, I have experimental data that suggests that, if you don't achieve levels of standardization, then the results of the complex analysis that sophisticated software can do today will be meaningless. That is because the variability of the sample is greater than the ability of the systems to measure. It's an example of the well-known adage: 'garbage in, garbage out.'

Impact of Ischemic Time

"Here's an example. We did one research experiment on the impact of ischemic time," he explained. "We wanted to know how shorter and longer ischemic times would affect our ability to analyze the critical molecules that are the target of the drugs in the clinical trial."

"We did a simple experiment to compare the results produced by a resection specimen and the biopsy specimen from the same patient," continued Feldman. "The resection specimen usually has one or two hours of ischemic time. The biopsy has almost no ischemic time. When an organ is removed, its blood vessels are clamped and tied before it is taken from the body. That entire process exposes the tissue to ischemia.

"We wanted to know what happens to the specific molecules that are the targets of the drugs being studied in the clinical trial," noted Feldman. "These are the molecules we need to measure.

"Is there a difference if I measure these molecules in a biopsy versus a resection sample?" he added. "We know that the very robust stains in the biopsy have almost zero expression in the resection specimen. There's a complete absence of the target molecules when the organ is taken out and compared with the biopsy sample. The range of intensity changes we saw was significant. Some tissue samples showed no loss of signals. Some have partial loss and some have complete loss.

"This issue is critical for laboratories," declared Feldman. "As a profession, we need to get our hands around how samples are handled. What are the best types of samples to be tested? What critical features need to be tracked as tissues are processed?

"The answer to each of these questions will have a profound impact on the amount of the protein or phosphoprotein epitopes that are present in the tissue we want to examine.

"The advanced pathology systems under development today have so much analytic sensitivity and precision that this tissue handling variability makes a huge difference," stated Feldman. "In the future, pathologists will no longer score these images as 1+, 2+, or 3+.

"Based on current standards of practice, we score them as discrete optical intensity units," he continued. "Now the difference between a 0.05 and 0.1 could be the difference between a response and no response from a drug.

Problem Of Variability

"This highlights the problem of variability," said Feldman. "If a specimen is handled in such a manner that this two-fold difference is masked, then the precision is lost because there was no control over the tissue.

"Here at UPenn, our experiments with the effects of ischemic time have triggered serious concerns," he concluded. "These experiments demonstrate that how the specimen is handled really makes a difference in the accuracy of the result produced from the analysis of that specimen.

"This has motivated us to launch research that we hope will answer these three questions: First, what causes ischemic time to produce a different measurement of the target molecules? Two, where in the analysis does ischemic time make a difference? Three, do these differences affect the accuracy of the analysis?

"Our investigations into these issues are just beginning," concluded Feldman. "Our first steps are focused on identifying all the sources of variation."

1970s, when pathologists introduced flow cytometry, we did one stain at a time. Over time, it became possible to do two stains at once—and then three, four, and more. Now it is routine to do flow cytometry with six color stains or more for routine clinical work.

"Biology doesn't happen one molecule at a time," observed Feldman. "There is an integration of information on and within cells that includes both positive and negative regulators. To understand what's going on in cells, it is necessary to look at more than one biologic pathway at a time.

"Hematopathology illustrates these principles and points us to the future of these concepts in surgical pathology," he added. "Will this also apply to clinical laboratory testing in the future? Yes, I have absolutely no doubt about that.

"However, at the moment, this type of work—translational research—is limited to clinical research," said Feldman. "During a clinical trial, when a physician gives a drug to a patient, we try to measure the response. That's one form of translational research.

"In doing translational research, as we develop and validate assays that become meaningful for routine clinical practice, these new assays will migrate from the research space and into wider use by clinical laboratories.

Beta Testing Begins

"Our working collaboration with CRi started about 10 years ago," he commented. "It was last year when we got this digital pathology robot system (Vectra). That's when we initiated beta testing.

Once this Pathology System Learns, It Can Continually Analyze Thousands of Images

PATTERN RECOGNITION and a machine classification system are at the heart of a sophisticated digital pathology system currently used for research purposes.

"The Vectra robot system from CRi gives us the capability to use numerous stains and biomarkers to perform very complex analyses of tissue," stated Michael D. Feldman, M.D., Ph.D., Associate Professor of Pathology and Laboratory Medicine at the Hospital of the University of Pennsylvania. "It can automatically map the areas of an image that have tumor and non-tumor cells.

"The pathologist teaches the system from these images," he continued. "For example, as it learns, I can continually refine its knowledge base. Upon achieving proficiency, I can then run tens of thousands of images through the system and it will work night and day without complaint or pause.

"This system is an imaging platform that is linked to the intelligent software," stated Feldman. "The robot scans slides at low magnification. The pathologist then uses these low magnification images—where the good fields of view are—to teach the system to find different tissue regions on the slide.

"Next, the system's software images the high magnification areas based on how it has been trained and how many fields of view need to be acquired to analyze the slide," he continued. "The system then fetches a pathologist-determined number of high-resolution fields. It uses these fields to collect statistically relevant data which are output as cytometric results.

"It takes more than one field of view to determine if there are enough cellular events to be statistically meaningful," he added. "The tissue must be sampled at multiple areas to get an adequate number of data points. The flow cytometer is a good metaphor. A flow cytometer doesn't analyze 100 cells. Rather, it analyzes tens of thousands of cells.

"This sophisticated digital pathology system works in a similar way," observed Feldman, "Enough fields of view need to be selected from the tissue specimen to represent thousands of events. That way, the statistics will bear out positive and negative results. The automated system allows the pathologist to find those areas of interest and regions at low magnification and then pull them in at high magnification."

"The robot has shown us that we need to consider the variation from lab to lab in the handling and processing of tissue and make sure that our systems account for variation in staining and other variables in how we handle specimens," he added.

THE DARK REPORT believes that the research unfolding at the University of Pennsylvania provides a timely peek into the next generation of digital pathology systems and its potential to change clinical practices in surgical pathology. Feldman and his colleagues are demonstrating how robotics and software can automate many of the manual functions that require time when a pathologist evaluates an image.

Equally intriguing is the ability to assess multiple spectra and biomarkers within the same issue—and accomplish this with mathematical precision. Again, the research activities with the advanced digital pathology system in use at UPenn show that technology makes it feasible to achieve this level of performance today. Collectively, these developments point to an exciting and profitable future for anatomic pathology. **TDR**

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Lab Briefs

BECKMAN COULTER REPORTS EARNINGS THAT INCLUDE OLYMPUS

THERE WAS A BIG JUMP in fourth quarter revenue at **Beckman Coulter Inc.**, of Brea, California, which increased by 22% over the previous year, to $989.6 million.

This number included $120.2 million in revenue from the recent Olympus Diagnostics acquisition. Beckman Coulter spent $800 million in August 2009 to purchase **Olympus Corporation's** diagnostics systems business. For the quarter, Beckman reported a profit of $64.2 million, down from $75.1 million in the same quarter a year earlier.

For the year, total revenue at Beckman Coulter was $3.26 billion, an increase of 5.2% over 2008 results of $3.09 billion. The company said that, when the revenue from the Olympus acquisition was excluded, Beckman Coulter's total revenue for the year declined about 1%.

LABCORP EXPANDS ITS BILLING OPERATIONS IN GREENSBORO, NC

THERE MAY BE QUITE A JOB TUSSLE for laboratory billing personnel in Greensboro, North Carolina, home to **Spectrum Laboratory Network**. That's because **Laboratory Corporation of America** just announced plans to expand its billing center in Greensboro.

Last week, *The News & Record* of Greensboro reported that LabCorp was planning to consolidate billing operations and would add 350 new jobs in Greensboro. By late spring or early summer, LabCorp says it will move into an existing building in Greensboro and invest almost $4 million over the next three years.

The state of North Carolina offered LabCorp about $900,000 in incentives to move to Greensboro, in Guilford County. CEO David King told the newspaper that Guilford County has a larger job pool than what is available in nearby Burlington, NC, where LabCorp maintains its corporate headquarters.

However, because Spectrum Laboratory Network is already established in Greensboro, there is likely to be intense recruiting between the two laboratory companies for the pool of qualified personnel, particularly if they have extensive experience in laboratory billing, coding, and collections.

ANTHEM CRITICIZED AFTER RAISING PREMIUMS BY 39% IN CALIFORNIA

LAST WEEK'S NEWS that **Anthem Blue Cross Blue Shield,** California's largest for-profit insurer, would raise premiums by as much as 39% for some customers with individual policies, set off a firestorm of criticism.

The Obama White House weighed in, with Health and Human Services Secretary Kathleen Sebelius writing a letter to the Anthem president saying that Anthem needed to justify the premium increase.

In a written response to the administration, **WellPoint, Inc.**, the owner of Anthem, stated that the premium increases are based on the greater cost of medical services, along with an exodus of healthy consumers from these insurance plans. Further, WellPoint noted that only 25% of consumers with individual plans would see a rate increase of 39%. The average would be a 25% increase, with some customers actually getting a premium reduction.

In response to these actions, Anthem now faces two government hearings. A panel of the House Committee on Energy and Commerce has scheduled a hearing February 24. The California Assembly's health committee will convene a hearing one day earlier, on February 23.

Pathologists and laboratory administrators should take these collective events as a sign of a shift in the healthcare marketplace. The actions of for-profit insurers will be scrutinized with more intensity than ever before. Any sizeable increase in the cost of health insurance premiums by private payers may become a target for media coverage and government hearings and investigations.

MEDTOX REPORTS GAIN IN CLINICAL LAB VOLUME AS DRUG TESTING DECLINES

AS EXPECTED, THE ECONOMIC RECESSION was responsible for a decline of 9.9% in drugs-of-abuse test revenue at **Medtox Scientific, Inc.**, of St. Paul, Minnesota. The company released its fourth quarter and full year earnings last Wednesday.

In the laboratory segment, MedTox said that revenue from drugs-of-abuse testing decreased 9.9%, to $36 million from $40 million in the prior year, and 5.7% to $8.5 million from $9.0 million in the prior quarter. For the full year 2009, total revenue at MedTox was $84.1 million, a 1.98% decline from $85.8 million in 2008.

Revenue from existing drugs-of-abuse testing clients dropped 18% for the quarter and 24% for the year. With an unemployment rate hovering around 10%, employers are doing fewer drug screens. However, a strong sales performance generated almost 15% more business from new clients and that volume helped offset the recorded declines in specimen volume from existing clients.

What is a more interesting outcome at MedTox is the company's progress with establishing a clinical laboratory testing operation to compete for business in the greater Minneapolis/St. Paul metropolitan area. This program was launched in early 2008. In the second year of operation, MedTox reports full-year revenues of $22.9 million from clinical laboratory testing. This is up from $19.3 million for 2008. Clinical Trials Services (CTS) is a significant portion of revenue in this operating division.

UNIV. OF TORONTO APPLIES MICROFLUIDICS TO BREAST CANCER TESTS

DIGITAL MICROFLUIDICS IS THE TECHNOLOGY that researchers at the **University of Toronto** are using to develop a way to measure estrogen levels from samples of breast tissue that are up to "1,000 times smaller" than the current standard for analysis.

The technology utilizes a microchip to accomplish multi-step processing of the assay. By using electrical currents to move droplets around the microchip, the research team at the **Wheeler Microfluidics Laboratory** (WML) can allow solvents and other chemicals to process and dissolve a dried tissue specimen. Eventually all biological elements are removed and only droplets of estrogen remain. Researchers report that the measurement of estrogen by this method is accurate.

Aaron Wheeler, Ph.D., Director at WML, is excited about the potential for this technology to be used in clinical settings. "This is relatively new and hasn't been applied to much yet; certainly not applied to anything like what we've done here," he told reporters. "It ends up being a perfect format for working with messy clinical samples." Wheeler believes that the technology is probably about five years away from clinical use.

Current technology in breast cancer testing for estrogen levels requires a 500-milligram biopsy, described by one source as "about the size of a Tootsie Roll." Patients must undergo anesthesia and there is a risk of scarring. This is why researchers at WML hope to develop a method which can produce an accurate estrogen result from a much smaller tissue specimen collected, for example, by fine needle aspiration (FNA). TDR

INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

In response to the skyrocketing expenses associated with genetic and molecular testing, health insurers are planning ways to control both utilization and the prices at which these tests are reimbursed. For example, during the past year, **Humana** began using **DNA Direct** of San Francisco, California, to preauthorize expensive genetic and molecular tests, while also advising physicians and counseling patients on their appropriate use. Pre-authorization of genetic testing may be the next big thing in medicine. On February 5, **Medco Health Solutions** acquired DNA Direct. Medco is one of the nation's largest pharmacy benefits managers (PBMs). Medco stated that it wanted to integrate DNA Direct's "physician, client, and patient support services" in genetic and molecular testing with its "growing portfolio of personalized medicine capabilities."

ADD TO: *GENETIC & MOLECULAR TESTS*

More payers are requiring pre-authorization of genetic and molecular tests. Clinical laboratories and pathology groups should be responding to this trend to protect their access to patients and maintain their ability to provide these tests. Michael Snyder, President of **Laboratory Management Services, LLC**, says this will be one of the most significant changes in managed care contracts between payers and laboratories during 2010. He will provide information on this trend, along with effective strategies at the upcoming *Executive War College* on April 27-28, 2010, in New Orleans.

CORRECTION:

In reporting the changes and the new equity owners at **Pathology, Inc.**, of Torrance, California, in the January 25, 2010, issue of THE DARK REPORT, the role of **England & Company** was not properly credited. England & Company acted as the exclusive adviser to the investor group, which included **ABS Capital** and **ORIX Venture Finance LLC**.

TRANSITIONS

• **Philip Chen, M.D., Ph.D.**, resigned from **Sonic Healthcare USA** at the end of 2009 to pursue other opportunities. Chen founded **Cognescenti Health Institute, LLC**, in Orlando, Florida, and sold the laboratory testing company to Sonic Healthcare in 2006.

That's all the insider intelligence for this report. Look for the next briefing on Monday, March 8, 2010.

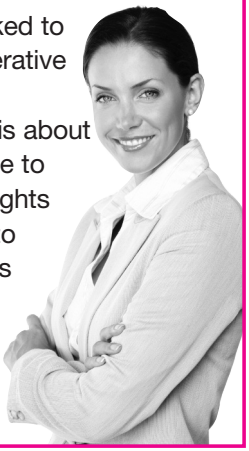
Make plans Now!

EXECUTIVE WAR COLLEGE

April 27-28, 2010 • Sheraton Hotel • New Orleans

Preview–Pat Wolfram, Ignis Systems:

LIS-to-EMR Interfaces & "Meaningful Use" Attract Profitable New Outreach Clients



You know that billions in federal money is earmarked to motivate physicians to adopt EMRs! It's now imperative that every clinical lab and pathology group have a productive EMR strategy. Plus, "Meaningful Use" is about to become the best point of leverage a lab can use to attract new outreach clients. Get the essential insights you need. Discover the overlooked opportunities to better serve doctors—and earn their loyalty. This is the "A-to-Z" you need on LIS-EMR interfaces and "Meaningful Use!"

Check for program details and to register!

visit www.executivewarcollege.com

UPCOMING...

- ***Major New National Reference Lab Company Prepares to Build Lab Facility, Initiate Operations.***
- ***EMR Donations as the Source of Competitive Leverage: Why Local Pathology Groups Are Handicapped.***
- ***So Your Lab Wants to Become ISO 15189 Accredited: Understanding Benefits and Pitfalls of the Process.***

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