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From the Desk of R. Lewis Dark...

THE DARK REPORT

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

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COMMENTARY & OPINION by...

R. Lewis Dark
Founder & Publisher

Clinical Labs and Whole Human Gene Sequencing

CLINICAL LABORATORY ADMINISTRATORS AND SENIOR EXECUTIVES would be well advised to pay close attention to our lead story about the whole human genome sequence collaboration just announced by the pathology department at **Beth Israel Deaconess Medical Center** (BIDMC) and **GenomeQuest, Inc.** *(See pages 3-6.)*

Together, the two organizations intend to be among the first in the nation to take the latest technologies in rapid gene sequencing and multi-gene analysis and develop laboratory assays for cancer and other diseases. Although the initial emphasis will be oncology—the traditional bastion of anatomic pathologists—I can foresee how pathologists at BIDMC are likely to quickly cross over into the domain of the clinical laboratory.

Until the past decade, the division between clinical pathology (CP) and anatomic pathology (AP) has been rather clear and distinct. The research and development work about to unfold at Beth Israel Deaconess Medical Center has the potential to muddy those distinctions. In fact, BIDMC's Pathology Chair, Jeffrey Saffitz, M.D., Ph.D., now envisions a "primary-care pathologist" who will use information in the whole human genome to make sophisticated diagnoses in ways unimagined until recently.

Reflecting on Saffitz' reasons why this is likely to become feasible, I can foresee that the primary-care pathologist will work in the clinical laboratory and use such technologies as rapid gene sequencing and multi-gene analysis to provide referring clinicians with very early and very sensitive diagnostic information.

If you agree with Saffitz that whole human genome sequencing can, at some future point, give pathologists a sophisticated and highly-accurate ability to predict disease, to diagnose disease, and to precisely guide therapeutic decisions, then it is reasonable to assume that this activity will take place in the clinical laboratory in preference to the anatomic pathology laboratory.

That is why, for my money, the BIDMC/GenomeQuest collaboration needs to be watched because it is a credible effort by very smart physicians and scientists to understand the information contained in a whole human genome sequence and convert that to actionable diagnostic, therapeutic, and predictive knowledge that directly benefits a patient. As this happens, I believe it is clinical laboratories which will take the lead role in providing these type of tests to the nation's office-based physicians. TDR

"Primary-Care Pathology" One Goal at Beth Israel

Pathologists to use whole human genome sequences for diagnosis and to advance personalized medicine

CEO SUMMARY: In a pioneering collaboration, the pathology department at Beth Israel Deaconess Medical Center in Boston, Massachusetts, will work with GenomeQuest, Inc., to perform whole genome sequencing of tumor specimens. GenomeQuest will handle sequencing, assembly, and annotation of the genetic data. BIDMC will analyze these whole human genome sequences to develop companion diagnostic tests and to find new ways to advance personalized medicine.

IN WHAT SEEMS TO BE THE FIRST COLLABORATION of its kind in anatomic pathology, pathologists at **Beth Israel Deaconess Medical Center** (BIDMC) in Boston, Massachusetts, are partnering with a genetic data management company to use whole human genome sequences for diagnostic purposes.

What adds excitement to this innovative collaboration is that the participating pathologists believe their pioneering work may lead to what they call the "primary-care pathologist." From the birth of an individual, pathologists would use their analysis of that individual's whole genome sequence to prevent disease, optimize health, and guide the care team.

Earlier this month, BIDMC pathologists and **GenomeQuest, Inc.**, of Westborough, Massachusetts, announced an innovative two-year agreement. Essentially, as the pathology department at BIDMC does whole human genome sequencing and multi-gene analysis, GenomeQuest will provide sophisticated support in whole-genome data management and analysis.

In recognition of the importance of informatics support for the whole genome sequencing effort, GenomeQuest "will also provide API [Application Programming Interface] access and training to the [BIDMC] department's scientific investigators and applied mathematicians."

Pathologists at BIDMC want to use whole genome sequencing of tumors as a way to develop useful diagnostic information. GenomeQuest will perform the sequencing, assembly, and annotation of entire genomes from the tumor specimens collected at BIDMC. Beth Israel pathologists will then take that information and interpret it.

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"We think that the landscape of molecular diagnostics is going to be revolutionized by genomic approaches—rather than by analyzing one or two genes at a time," observed Mark Boguski, M.D., Ph.D., and Associate Professor of Pathology at BIDMC. Boguski also serves in the Center for Biomedical Informatics at **Harvard Medical School** (HMS) and has been described as "one of the fathers of computational biology."

"As the diagnosticians of medicine, pathologists are responsible for all the other laboratory tests," added Boguski. "We consider a genotype to be no different than any other lab specimen that we get."

Boguski points out that, since 1990, when the whole human genome sequencing project commenced, the popular wisdom was that the medical benefits from the human genome project "were largely couched in terms of new therapeutics."

Diagnostic Applications

Boguski and his pathologist colleagues at BIDMC believe that the major first clinical fruits from whole human genome sequencing will actually come from diagnostics, not therapeutics. "In the last couple of years, we've come to the realization that whole genome sequencing is going to make its biggest, earliest impact in precision diagnostics for personalized medicine."

"Further, we think that the landscape of molecular diagnostics is going to be revolutionized by genomic approaches rather than by analyzing one or two genes at a time," he declared. "This has implications for personalized medicine because you can't personalize medicine until you get a very precise diagnosis—not only for that patient, but for that patient's disease at some point in time.

"Keep in mind," said Boguski. "A lot of diseases change over time, and so precision diagnosis happens multiple times within the course of a patient's disease. It's going to be absolutely essential."

Boguski had another observation about how whole genome sequencing can be transformational to laboratory medicine as it has been practiced for the last 100 years, stating, "I recently read a statistic that 70% of clinical decisions are based on laboratory values. Now we have a whole human genome sequence to use as the new laboratory value and it has more information in it than the combination of many existing laboratory assays!

Precision Diagnosis

"You can't have personalized medicine without precision diagnosis, and increasingly that diagnosis is going to be multifactorial, based on whole-genome data sets," he emphasized.

"There's another aspect to this," continued Boguski. "Traditionally as pathologists, we get involved when somebody becomes sick and a clinician sends us a specimen to diagnose a disease.

"But increasingly, well patients—and very likely newborns—will have their genomes analyzed," he noted. "The role of pathologists will not simply be to diagnose disease, but also to help develop health maintenance plans, to prevent disease, and to participate in the lifelong management of individual healthcare in an effort to preserve health.

Primary-Care Pathologist

"Here at BIDMC, we discuss the idea of the "primary-care pathologist" and we see this as a model for the future," Boguski added. "This is a new role for us and I think it's one that the pathology profession must aggressively embrace. In this way, whole human genome sequencing redefines pathology's future mission."

Pathology leaders at Beth Israel Deaconess have a razor-sharp focus on the goal of this new genomic research initiative. They are concentrating solely on the parts that will result in putting usable gene data in front of physicians at the point of

Creating a Clinical and Business Model to Support Diagnostic Use of Whole Genome Screening

"WE ARE AN ACADEMIC MEDICAL CENTER and a tertiary-care facility," said Jeffrey Saffitz, M.D., Ph.D., and Chairman of the Department of Pathology at Beth Israel Deaconess Medical Center (BIDMC). "But when it comes to whole human genome sequencing, we also are an institution with limited capital resources.

"Our clinical laboratory lacks access to the resources required to purchase multi-million-dollar sequencing machines and to develop a super-computer center for doing whole human genome sequencing," he explained. "In order for us to provide what we anticipate will be essential clinical services to our doctors, we have come up with a different approach.

"Using collaborations like the one with GenomeQuest, we can access the latest technology and tap into the most powerful sequencing and analytical resources available," noted Saffitz. "We can then tailor the resulting flow of diagnostic information to the needs of our physicians and their patients.

"This is not necessarily the model that will prevail at every institution in the future," he continued. "But we envision a future in which every community hospital clinical lab will have the capacity to do this type of testing and analysis.

"At this early stage in genome sequencing, we are using this outsourcing model to leverage our existing resources," Saffitz noted. "Frankly, we also question whether we need to do all this sequencing in-house."

"What we are doing here at BIDMC is meant to be a portable and sustainable model," added Mark Boguski, M.D., Ph.D., and Associate Professor of Pathology at BIDMC. "If this is really going to be part of standard-of-care medical practice, basing it on a big-box genome center right next door is just not viable economically.

"So, as we move forward, we are taking a very business-process-oriented approach to this area of lab science, while working to answer this question: 'what would it really take to pull this off in 5,000 hospitals across the country if it becomes the standard of care?'" declared Boguski. "Developing a viable model that can be adopted in other clinical environments is part of the experiment here."

care. They expect to deliver a highly-advanced, evidence-based diagnosis.

"This is a stepwise process," explained Jeffrey Saffitz, M.D., Ph.D., and Chairman of the Department of Pathology. "In order to bring this into medical practice we've developed a model that involves using whole genome sequence data in clinical practice.

"To get there, this model involves a considerable amount of outsourcing," Saffitz noted. "We don't want to be the ones who do the sequencing, and we don't want to be the ones who do the initial data annotation. Rather, we want to interpret the data and help clinical physicians use this genetic information in the context of all the other things going on in diagnosis and treatment of the patient.

"We have partnerships with members of the technology community who are leading next-generation sequencing companies," he continued. "These companies can do the sequencing far better, much more rapidly, and much more economically than any research institute or hospital laboratory.

"Our new partnership with GenomeQuest is the next step and gives us access to the data in a form that we can analyze," explained Saffitz. "Our view is that pathologists in the future won't be inputting gene sequence data. We will be dealing, first, with specimen control and, second, with data interpretation. Both of these activities are primary to the role of the pathologist."

Boguski observed that demand for whole human genome sequence data is

growing from several sources. "Of course, pharmaceutical companies are already looking at ways to use genome-wide, genome-scale information to manage prescriptions to produce real cost-benefit value propositions," he stated.

"As well, people from the benefits management industry are saying that they're ready to use some of this information right now," continued Boguski. "Health insurers tell us 'we will pay for something where you can demonstrate value.'

"This will be one challenge in our effort," he added. "Our goal is to demonstrate how this new diagnostic approach will create value in healthcare.

"This value can come in several ways: 1) by directing the rational allocation of extensive resources; 2) by using the most effective therapy; 3) by getting away from this trial-and-error approach; and, 4) by minimizing side effects and adverse outcomes," stated Boguski. "All of these things are ultimately going to save money for the healthcare system. So again, we have to begin with first steps. We can't do all this yet, but we see this coming."

Companion Diagnostics

One obvious target for the pathologists at BIDMC is to use the whole human genome sequence data to develop companion diagnostic assays. "Currently, companion diagnostics are characterized by individual, narrowly-focused technology platforms with a proprietary set of reagents," observed Boguski.

"However, in the future, molecular diagnostics will simply be software filters and algorithms applied to whole genome or transcriptome data," he said. "This work will fundamentally change the nature of what a companion diagnostic means for drug development."

Boguski recommends that clinical laboratories should take steps to prepare for these developments. "Every clinical lab should be bringing its staff up to speed on genomics technology and its applications in clinical diagnostics," he advised. "We are developing residency training programs, and there is early talk about CME programs for people who are already practicing out in the community.

"At this point, pathologists and laboratory professionals should keep an eye on the technology providers because there will be a time when it will make sense for them to start to gain access to this technology," he continued. "And it probably will be an outsourcing model at first, because that's the most cost-effective way." TDR

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Training New Pathologists With Genomics Curriculum

PATHOLOGISTS AT BETH ISRAEL DEACONESS MEDICAL CENTER took the lead in developing a genomics training curriculum for residents in pathology programs. It has gained significant national traction.

Several meetings took place at BIDMC during which the key players in pathology—residency, education programs and other participants—came onboard to this goal. According to Mark Boguski, M.D., Ph.D., he and Jeffrey Saffitz, M.D., Ph.D., Chairman of the pathology department "have thrown down a challenge" to the pathology community to have, by 2012, a genomics and personalized medicine curriculum as part of every pathology training program in North America and in all ACGME-approved pathology residencies.

"We think this is an achievable goal," he said. "And we've already made considerable progress. It's very important that, as a discipline, pathology stands up and says, 'we will prepare the future practitioners to function in this new world.'

"This will be key for helping the pathology profession maintain a leadership position in this new age of personalized medicine," concluded Boguski. "For that reason, the genomics education component is absolutely crucial."

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Q3 Earnings Are Mixed Bag For the Two Blood Brothers

Consistent with earlier guidance, Quest Diagnostics reported its third consecutive quarterly volume decline

IF THERE IS A NOTABLE EVENT in the laboratory testing marketplace during 2010, it is that one of the nation's billion-dollar lab testing behemoths has reported three consecutive quarters of declines in the number of test requisitions it handled, when compared to the same quarters during 2009.

In the memory of THE DARK REPORT, one would have to go back to the 1990s to find a comparable year when any of country's largest public laboratory companies reported a multi-quarter decline in patient requisitions. Certainly since the year 2000, neither **Quest Diagnostics Incorporated** nor **Laboratory Corporation of America** has ever reported such an unbroken string of quarterly declines in specimen volume.

Investors were not surprised when, during its third quarter earnings conference call, Quest Diagnostics Incorporated reported a slight decline in specimen volume. The company said that patient requisitions were 0.3% less in the third quarter, compared to the same quarter in 2009. This was consistent with its earlier guidance to financial analysts.

Third Quarter Performance

For third quarter, Quest Diagnostics also reported that its revenue of $1.86 billion was 1.7% less than Q2-2009 revenue of $1.90 billion. Revenue per requisition declined by 1.3% from the previous quarter in 2009, but was unchanged compared to second quarter 2010. These numbers were also consistent with earlier guidance that Quest Diagnostics had provided to Wall Street.

Meanwhile, at LabCorp, the numbers moved in a more positive direction. For example, LabCorp reported that specimen volume, as measured by requisitions, increased by a more typical 3.0% for the third quarter, compared to Q3-2009.

Decline In Specimen Volume

Like Quest Diagnostics, LabCorp had reported declines in specimen volume for both the first and second quarters of 2010. LabCorp's declines in the number of patient requisitions were 3.0% and 2.0% for the first and second quarters, respectively.

LabCorp's revenue increased by 7.7%, from $1.18 billion in Q3-2009 to $1.27 billion in Q3-2010. Revenue per requisition increased 2.5% during the same period.

It is interesting to speculate about why Quest Diagnostics is experiencing a string of quarterly declines in the number of patient requisitions it handles, particularly since it has been more than a decade since any similar pattern was reported by a major public laboratory company.

Two factors are different in 2010 compared to other years of the past decade. One factor is the sluggish economy, which is only marginally stronger in 2010 than it was in 2009. The popular wisdom has been to attribute declines in specimen volume throughout 2010 to the reduced number of patient visits to office-based physicians. *(See chart on page 9.)*

During second quarter conference calls in July, both lab companies discussed the drop-off in patient visits to physicians' offices as one reason for the declines in patient test requisitions during the quarter. *(See TDR, August 2, 2010.)* However, during the third quarter, LabCorp enjoyed a 3% increase in patient requisitions while Quest Diagnostics saw the small reduction of .03%.

As a point of comparison, when **Bio-Reference Laboratories, Inc.** (BRLI) announced its fiscal third quarter earnings for the quarter ending July 31, 2010, it reported a healthy increase in patient requisitions. BRLI said that patient requisitions had grown 17%, climbing from 1.2 million in Q3-2009 to 1.5 million in the current quarter. Similarly, **Sonic Healthcare, Ltd**, of Sydney, Australia, disclosed that, for its full fiscal year ending on June 30, 2010, its laboratories in the United States posted organic revenue growth of 6.3%.

Strong Growth Rates In 2010

Thus, throughout 2010, two of the larger lab competitors serving physician offices have reported positive increases in specimen volume. This is a stark contrast to the three consecutive quarters of fewer patient requisitions at Quest Diagnostics.

Lab acquisitions—or the lack thereof—is another market dynamic in 2010 that is different from the past 12 years. Quest Diagnostics has not done a sizeable laboratory acquisition since it closed its purchase of **AmeriPath, Inc.**, in May, 2007. This falls outside Quest Diagnostic's laboratory acquisition pattern of the 1997-2007 period.

Thus, for the past 40 months, the primary source of new specimens for Quest Diagnostics would be its internal sales and marketing programs. During this time, direct competitors in major markets, including LabCorp, Bio-Reference Labs, and Sonic Healthcare, have been busy working to woo away clients of Quest Diagnostics.

But another market dynamic may be contributing to a steady erosion in the number of patient requisitions flowing into Quest Diagnostics. Around the nation, in major cities and rural towns, a host of hospital laboratory outreach programs are working diligently to win physician clients away from the two blood brothers.

Hospital Lab Outreach Trend

Wall Street may be underestimating the influence and market impact of the nation's hospital laboratory outreach programs. Informed pathologists and laboratory administrators know two things about the hospital laboratory outreach trend.

First, each year, the specimen volumes at the most successful hospital laboratory outreach programs grow at double-digit rates. Quietly and off the record, these hospital laboratory outreach programs often confirm that a large number of the new clients brought in by their sales force were formerly clients of either of the two blood brothers. This is to be expected, since the combined market share of Quest Diagnostics and LabCorp is dominant in most regional markets across the United States.

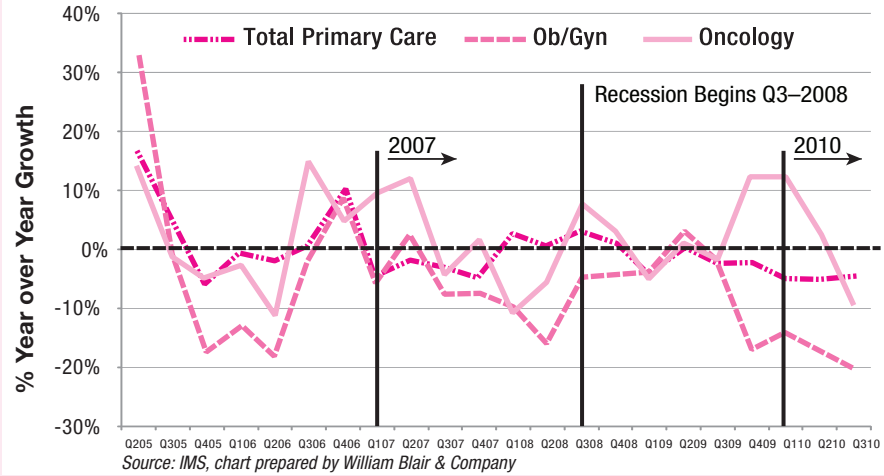
Second, and equally interesting, is the fact that, in every year since the late 1990s, more hospitals and health systems have initiated a laboratory outreach testing program. Thus, the number of hospitals competing for the test referrals of office-based physicians in 2010 is significantly larger than it was, say, in 2000.

More Lab Outreach Today

To illustrate this principle, assume that there were 200 professionally-operated hospital laboratory outreach programs in the year 2000. Assume that, in the year 2010, there are now 500 hospital lab outreach programs. This implies that, not only are the two blood brothers directly confronted with more lab competitors, but these competitors are operating in a larger number of regional sub-markets across the nation. One might describe this competitive pressure against the two national laboratories as "death by a thousand cuts."

Growth in Physician Office Visits by Specialty

Showing Percent Increase/Decrease by Quarter from Q2-2005 through Q3-2010



Source: IMS, chart prepared by William Blair & Company

THIS CHART SHOWS THE PERCENT CHANGE IN THE QUARTERLY YEAR-OVER-YEAR GROWTH OR DECLINE in the number of physician office visits for the specialties of primary care, ob-gyn, and oncology for the years 2005-2010. One interesting observation is that, during this five-year period, the trend was mostly down. Primary care office visits increased in only nine of 22 quarters. Ob-gyn office visits increased in just four of 22 quarters. Oncology office visits increased in 13 of 22 quarters, probably because patients with cancer have a motive not to delay diagnosis and treatment.

The other useful insight is that, since the beginning of the recession in the second half of 2008, the number of patient visits to primary care and ob-gyn offices has consistently declined when compared to year-over-year periods. The drop-off in patient visits to physician offices in 2010 appears to continue a general declining trend established as early as the second half of 2007.

Certainly "death by a thousand cuts" describes the steady erosion of histology and anatomic pathology case referrals experienced by the two blood brothers, as many physician specialty groups build in-house pathology labs. Both national lab companies publicly acknowledge that this single market trend has retarded their growth of specimen volume in anatomic pathology case referrals in recent years by a noticeable amount.

Thus, couldn't it be equally true that the collective sales efforts of hundreds of professionally-operated hospital laboratory outreach programs now similarly eat into the total number of specimens reaching the two national laboratories from physician office referrals?

If the scenario described here by THE DARK REPORT is accurate, it means hospital lab outreach programs are responsible for a measurable portion of the decline in patient requisition volume reported by the two national laboratories during 2010. That would be a factor as yet unrecognized by either the lab industry or Wall Street.

It is notable that, after more than a decade of aggressive growth, 2010 has proved to be a challenging year for the national lab companies. With continuing growth in the number of hospitals launching a serious laboratory outreach program, this portends more intense competition for the lab test referrals of office-based physicians in coming years. TDR

CEO SUMMARY: For more than three years, pathologists at Washington University in St. Louis have worked with several different scanning products and digital pathology systems. Step-by-step, the Pathology Department has learned important lessons in how to capture digital images, archive them, then make them available on demand to the pathologists. WU currently captures images from about 25% of its surgical pathology cases and is making progress with the use of digital image assessment (DIA) to advance patient care.

Digital pathology systems used at Washington University for three years

Growing Role for Digital Image Analysis in Pathology

DIGITAL PATHOLOGY IS EXPECTED TO BE both transformational and disruptive to the profession of anatomic pathology. For many surgical pathologists, this is not welcome news.

After all, such pathologists have decades of experience in the use of glass slides and microscopes. In this country, these are the tools that pathologists use to deliver a diagnostic service that is the envy of the world.

But, for many of the right reasons, digital pathology is poised to become the technology platform that allows pathologists to further advance the field of laboratory medicine. Use of digital whole slide images (WSIs) and sophisticated software algorithms will become essential complements to the skills and scientific savvy of surgical pathologists. Physicians and patients will benefit from the increased sensitivity and accuracy that results from use of these rapidly-evolving technologies.

To gain an early peek into this brave new world of digital pathology, THE DARK REPORT recently caught up with one of the nation's most respected academic pathology departments. For more than three years, the Pathology Department at the **Washington University School of Medicine** (WUSM) in St. Louis, Missouri, has used the digital pathology systems and products from several different manufacturers. Few pathology labs in the world have the hands-on experience found at WUSM that comes from working with the digital pathology systems from different vendors.

At Washington University, pathologists are bullish on the future of digital pathology. "From this point forward, digital pathology will definitely play an expanding role in laboratory medicine," stated John Pfeifer, M.D., Ph.D., who is a Professor of Pathology and Immunology at WUSM. He is also the department's Vice Chairman for Clinical Affairs and a Professor of Obstetrics and Gynecology. "But digital pathology is a developing technology, which means it has limitations."

In this exclusive interview with THE DARK REPORT, Pfeifer discussed at least four major insights that he and his colleagues have developed from their work with whole slide imaging and digital pathology systems.

First, the WUSM pathologists have come to better understand how the human mind works—given its evolutionary development—and how digital pathology can work in complement with the pathologist's intellect and clinical experience.

Second, WUSM pathologists are learning how to use "digital image assessment" (DIA) to extract more information from the whole slide image. In turn, this provides enriched diagnostic information to the pathologist and opens the door to a more sophisticated analysis of the WSI.

Third, WUSM pathologists are expanding the capabilities that WSI and DIA can deliver in support of the pathologist. But they recognize that the current state of the technology will channel use of digital pathology toward specific functions.

The fourth insight relates to the performance of the current generation of digital pathology systems.

In discussing the first insight, Pfeifer noted that it is important to know how the human brain works with images. He offered a Darwinian metaphor about the human mind, including how human eyes "see" and how the human brain processes those images. This is a necessary starting point for the reader to understand Pfeifer's predictions about how the pathology profession will take up and use whole slide images and digital pathology systems.

Human Visual Processing

"Bear with me for a moment," asked Pfeifer. "Think about the human hunter, crouching in the jungle. He strains to distinguish his prey from the dense, leafy background of his surroundings. This is how human visual processing evolved over hundreds of thousands of years.

"At this time—when we were all hunters in the wild—our visual processing system did not evolve around the coat color of our prey in the wild," he observed. "Human hunters had very few discussions about whether the color of the animal's coat was sandy or brown—or whether the intensity of the hue was more red than yellow.

Seeing Patterns, Boundaries

"Instead, our visual system evolved around contrast boundaries and pattern recognition," explained Pfeifer. "Humans are hard-wired to see the edge of a grass blade or the outline of a tree branch so that an animal crouching behind it can be seen.

"The point is that human brains process information based on the way our visual system evolved to help us recognize animals hiding in the grass and *not* by distinguishing between the color or the intensity of the grass itself.

"Accept this premise about how the human eye 'sees' and how the human brain processes that image, and it becomes easier to understand why digital pathology systems can function in ways that expand the pathologist's ability to tease out all types of clinically-useful information from the whole slide image," he continued. "More specifically, this is where the role of digital image assessment (DIA) comes into play.

How Pathologists "See"

"Let's take the example of quantitative or semi-quantitative analysis of immunohistochemical stains and how pathologists process this information," Pfeifer noted. "I have a collection of images showing that—if you mask them in certain ways—you would call the color on that image a five on a scale of one to 10 because it is in the mid range.

"However, were you to mask that same color in a different way—by using a vertical mask or a horizontal mask—you might say it is only a two out of 10," he commented. "It is the same intensity of color. Nothing else has changed except the mask and it is the mask which affects how our brains process the information.

"In general, we tend to think that pathologists are very good at identifying something that's negative and when something is intense, pathologists call it intense," he added. "But in the middle range, there is a lot of variability between pathologists.

"More specifically, it is becoming clear that there is significant variability between each pathologist day-to-day," continued Pfeifer. "Lighting conditions and many other variables, including the quality of the imaging systems and microscopes, can contribute to this variability.

"The point is that pathologists are not very good in the middle areas because humans are not very good in the middle regions," Pfeifer said. "That's why digital image assessment has the potential to help pathologists in the middle regions."

Hard-Wired To Be Correct

Pfeifer now discussed the second important insight gained from the use of digital pathology systems at Washington University. "DIA is an improvement because it is hard-wired to be correct," he stated. "Compared to humans, DIA can be much better at distinguishing differences in the middle areas because DIA can be programmed both: 1) to recognize the prey crouching in the grass; and, 2) to precisely and objectively measure the color and intensity of the hue of the grass.

"DIA systems offer another benefit," added Pfeifer. "They can be standardized in ways that other instruments, including microscopes, cannot.

"We now have reached the point in the conversation where pathologists become uncomfortable," noted Pfeifer. "That is because we are talking about buying machines to do what pathologists do.

"While that idea may make pathologists uncomfortable, having machines do this work produces two distinct advan-

Because They Tend To Be 'Lone Wolves', Pathologists May Need Custom Software to Work With Digital Images

"INSTALLING A DIGITAL PATHOLOGY imaging system in a large academic medical center may require custom software to ease the transition to the new system for all pathologists on staff," stated John Pfeifer, M.D., Ph.D., Professor, Pathology and Immunology, at Washington University School of Medicine in St. Louis, Missouri. When the Pathology Department at the School of Medicine wanted to get the most from its digital imaging systems, it needed custom software.

"We have about 25 to 35 people who sign out pathology cases," he explained. "And academic pathologists are lone wolves. Each one has an individual style. Some are early adopters and some are never adopters. This makes it very difficult to tell these people in academic medicine that they need to do something one way if it's difficult to work that way. For our practice, it meant we had to develop various interfaces to make the digital pathology system work for each of our pathologists.

"Clinical labs have a laboratory information system (LIS) to open up reports, sign out reports, and issue reports," continued Pfeifer. "But for digital imaging, another software program may be needed with separate passwords and log-ons for viewing scanned images.

"It's likely that the second program will run in the background— but it will require a second monitor on the pathologist's desk," he noted. "This change in work practice might mean some pathologists will not use the ability to view images digitally.

"To solve this problem, we worked with our digital imaging and LIS vendors to write separate interfaces for our pathologists," explained Pfeifer. "Now we have a system that everyone can use. So if the pathologist is using **Cerner** CoPath to write a report, he or she will see a tab in the background.

"Clicking the tab instantly opens an interface to the digital imaging software. A second mouse click brings up the specific pathology image," stated Pfeifer. "To write this interface cost about $50,000 but it was worth the expense because it established seamless work flow on the desktop for our pathologists.

"Here's how it works," he explained. "When a pathologist needs to sign out, for example, a case of an excision, the system will tell him or her if there is a previous case for this patient. By clicking a tab, the pathologist sees—in half a second—that four slides from that previous case are available to view digitally. By clicking on a slide, the system opens the digital image to allow the pathologist to navigate to it.

"This means that pathologists use just one monitor and log into only one system each morning," Pfeifer said. "They don't have to remember different user names and passwords for the different systems. It is seamless. Before we got this interface, there were about three of us who were willing to work without it. But now that we have this interface, everyone uses it, and we all love it."

tages," he observed. "First, anyone looking at a substantial number of HER2/neu immunostains would welcome having a computer to help them do this work. After all, it can be repetitive and uninteresting.

"Second, pathologists using a digital pathology system will continue to issue a report based on their analysis of the specimen," he affirmed. "They will use laboratory techniques to get the right answer and will continue to bill for the technical and professional components of this work. The only difference is that computer image analysis will help the pathologist make the analysis.

"Just as they do now, pathologists must still identify the area on the slide to be scanned and determine if specimen is positive for HER2/neu, for example," he said. "The pathologist remains essential to the diagnosis. It's just that computers will contribute more precision and accuracy to the pathologist's findings.

"These are the reasons why whole slide imaging is a market niche poised to grow rapidly," observed Pfeifer. "When DIA becomes mainstream, it will become possible to sell digital slide scanners to all of the 4,800 hospitals nationwide because they will need it to do standard pathology.

"There is a big difference between writing image analysis software that can quantitate a level of immuno-staining and writing software that can recognize a pattern of cells and tell you whether it is cancer or not."

"Currently, digital pathology is most commonly used in niche applications," he noted. "WSI has a role in conferences, for telepathology, and for moving images across cities or continents. Here at Washington University, we continually learn more about how to use WSI and digital image analysis in ways that improve our analysis of specimens."

Next comes the third insight about digital pathology. In their work with digital pathology systems, pathologists at Washington University believe that WSI and DIA will have a very defined role. Pfeifer explained that "there is a big difference between writing image analysis software that can quantitate a level of immuno-staining and writing software that can recognize a pattern of cells and tell you whether it is cancer or not.

"For example, if you work at it, you can develop DIA specific to defining one disease, one kind of condition, and one type of specimen, such as with Pap smears," he noted. "But that's a long series of ifs: if you have one disease, if you have one type of stain, and if you have a standardized preparation. Were you to set up the DIA to handle all these boundaries, you can make it work.

Developing DIA Solutions

"The practical challenge for DIA pathology is the fact that thousands of biomarkers have been identified, many different stains are available, and the tumors have similar patterns but the background cells have a lot of variety," observed Pfeifer. "It becomes a complicated process to develop a DIA application for each one of these unique combinations. For this reason, I don't see DIA being used to support automated diagnosis by computer. That may be decades away.

"On the other hand, I do see DIA being used for quantitating immunostains," he said. "This is what pathologists do with telepathology. A glass slide is scanned and the image is put on a computer screen. The pathologist then makes a diagnosis off that image on the computer screen. That's different from taking a scanned image and having a computer make a diagnosis based on that image.

Building Into the Future

"That is my take on the future of DIA," said Pfeifer. "However, remember, the field of digital pathology is in its earliest stage in terms of the evolution of image analysis. At our lab, we have only three years of experience at scanning slides. Every day, we learn more about how these systems work and about some of the challenges they present to pathologists."

Next, Pfeifer turned to practical lessons learned by the pathologists at Washington University. "There are certain realities with introducing a slide scanning system," he said.

"The first lesson is that it requires a significant capital investment," advised Pfeifer.

Digital Pathology Systems Help Boost Academic Center Role for Patient Referrals

ONE USE OF DIGITAL PATHOLOGY SYSTEMS at the Washington University School of Medicine in St. Louis is to support the academic center's role in patient referrals. John Pfeifer, M.D., Ph.D., Professor, Pathology and Immunology at the Washington University School of Medicine, in St. Louis, explained how the university uses whole slide imaging (WSI).

"Before acquiring image scanners and digital pathology systems three years ago, we rigorously evaluated how we would use digital pathology and where it would add value," he recalled. "We discovered it could help us in several places, such as consults where institutions want their pathology slides returned after the consultation.

"We need a permanent record whenever a case comes here," explained Pfeifer. "We review the case, issue a report, and maybe two months later, the patient ends up coming here for definitive therapy.

"At that time, we can compare our archived digital image of what was on the definitive excision from what was there initially," commented Pfeifer. "This is especially important in those cases where there is a difference. Use of digital images enhanced our clinical practice by allowing us to have a permanent record of these slides. This is a big deal, because there are many consults and everyone wants the slides returned to them.

"The other need we have is that patients are often presented at conferences even before they come to our academic center for definitive care," he said. "We need digital images to project at those conferences.

"One area that is growing in volume and which makes digital imaging incredibly helpful is ancillary testing modalities that result in the destruction of the slide," Pfeifer stated. "Many molecular testing paradigms result in destruction of the sample.

"When this happens, the question comes up about whether there was a specimen mix, or a contaminant, or perhaps it was very small tumor that was present only on the biopsy," explained Pfeifer. "When you collect tissue off that slide, it is obviously not going to exist in your files anymore. So we get a whole slide image of the slide and archive that image in our database.

"Then we can destroy the slide as part of testing because we have an electronic image of the slide," he added. "That is incredibly helpful because we used to fret about the destruction of these samples."

"We have slide scanners from **Aperio Technologies**, from **BioImagene,** and from **Trestle**. Since we work with a number of different vendors, we are not a company store.

"We also work with multiple informatics and systems vendors," he added. "As vendors, **Cerner Corporation**, which supplies our LIS, and **Aperio Technologies, Inc.**, which supplies Spectrum hardware and software, have been particularly responsive in helping us adapt their products to our specific needs.

"These vendor collaborations played an important role in helping us learn how to get the most out of their software and instrument systems," noted Pfeifer. "It is a reminder for all labs that one key to success is to have an effective, ongoing relationship with the vendors who supply information systems and analytical instruments."

Expense of Digital Pathology

Digital pathology systems are expensive. "Regardless of vendor, these systems cost about $100,000 to $200,000 or more,"

continued Pfeifer. "We estimate that the working life of these machines is about five years. Also, once installed, they are not free to operate.

"For a private pathology group, it will take as much as $250,000 to acquire the scanner and digital pathology system," explained Pfeifer. "There is a need to hire at least one person to care for the machine. This covers the cost to acquire and to operate the digital pathology system.

Cost To Store Digital Images

"It is important to also budget for the cost of storing the scanned images," he added. "We calculate that, based on our analysis of storage costs, it costs about 25¢ cents to put each image on a server somewhere. Since we will scan between 20,000 and 25,000 images this year, we will spend about $6,000 to $8,000 to store our digital pathology images on a server rack.

"One reason storage is so expensive is that these are very large image files," he said. "The size of the files depends on the region of the tissue being analyzed. The size of a file at 20x magnification could be 300 to 550 megabytes and at 40x, it could be 1 to 1.5 gigabytes in size. Those are huge image files.

"In addition to the capital costs of the machine, the personnel costs, and the direct cost of storing the images, a key component of the digital pathology system is the software that allows you to store the images, then retrieve them for viewing by the pathologists," stated Pfeifer. "Because it is software, your pathologists will be required to learn how to use it.

Lessons Learned

"This brings up the question of using off-the-shelf software versus customizing software that is tailored to the specific needs of your practice environment," he said. "Digital pathology vendors are willing to work with you in your practice environment, but there may be interfaces or some custom code that needs to be written and that will cost money. The benefits are significant because of improved workflow and the pathologist's ability to electronically move information to colleagues or referring physicians."

It is unusual for any pathology department or pathology group to buy and use multiple brands of scanners and digital pathology systems. Thus, the experience of Washington University pathologists over the past three years offers a number of unique insights and valuable lessons.

First, for a digital pathology system to be useful, the pathology laboratory needs to accomplish two things with equal proficiency. One is to establish a productive workflow to acquire the pathology image, archive it, and make it available on demand to the pathologist.

The other is the importance of an integrated suite of pathology informatics capabilities that support both the operational workflow in the lab and the pathologists' diagnostic practice patterns in a seamless manner.

Working With Digital Images

It is noteworthy that WUSM pathologists spent the resources necessary to allow pathologists to access and view digital pathology images in ways that were consistent with their individual practice preferences. Once this capability was in place, 100% of the department's pathologists began to regularly work with digital pathology images.

Another noteworthy insight is how digital pathology is now an essential component of the WUSM pathology department's consultation service. For subspecialist pathologists, this development points to one valuable way that use of digital images and digital pathology systems can expand their network of referring clinicians—and the revenue that comes with these additional consultations. TDR

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University Hospital's IT Director Outlines the Nuts and Bolts of Digital Pathology

IT WAS 2008 WHEN THE FIRST DIGITAL PATHOLOGY SYSTEM was put into use by the Pathology Department at the Washington University School of Medicine in St. Louis, Missouri. "It took our information systems department about nine months to build the capability and two months to implement the informatics infrastructure to support digital pathology," recalled Mike Isaacs, the Director of Information Systems, in the Department of Pathology & Immunology.

"In the first year, while everyone was learning how to work with digital pathology images, about 4,000 cases were scanned," he said. "Last year, that number increased to 9,500 cases. For 2010, we are on pace to scan about 12,000 images, which is about 35 cases scanned per working day this year.

"In the beginning, only different research projects and study sets were scanned," Isaacs noted. "Next, we began scanning slides to use in conferences.

Interface to Patient EMR

"One factor that limited the utility of digital pathology images was that our pathology informatics platform was not yet linked to the patients' electronic medical record (EMR)," he explained. "The digital pathology images resided in a Spectrum database but were initially not accessible from the Cerner CoPath laboratory information system (LIS). In 2009, we established an electronic link to the patients' records, went live, and did about 9,500 scanned images.

"It is important to know that, in 2010, the 12,000 scans represent just a small percentage of the total number of pathology cases, as well as about one quarter of the 42,000 surgical cases handled by the Pathology Department in 2009," noted Isaacs. "However, it is important to note that, in that 12,000 number is about 95% of all of our inside-outside consult cases.

"Remember that many of these cases will generate about 10 slides each," continued Isaacs. "Pathologists typically select two or three of the diagnostic slides for the digital image archive. Because the images are so big, before scanning slides, it is important that there be real benefit for later diagnostic purposes.

No Workflow Bottlenecks

"As mentioned, these are large images," observed Isaacs. "We are set up to scan about 1 gigabit per second from the scanner to the server. That is very fast—meaning there are no workflow bottlenecks as the pathologist waits for the system to produce the needed images.

"Another lesson is the need for one full-time person to manage the digital images," he stated. "In our arrangement, two people work part time and each does different aspects of the workflow. One gets the cases when they are scanned, reads the bar code to identify the patient and the test (such as the H&E slide), and then sends it to the Cerner CoPath LIS, where the system matches the bar code to the patient.

"Our second part-time staff member loads the scanner itself and chooses the correct area of the slide to scan," Isaacs said. "The goal is to avoid scanning the entire slide, where appropriate. If the region of clinical interest is smaller, the digital file of the scan is smaller.

"Once a digital image is captured by the scanner, this staff member checks the focus for the image," concluded Isaacs. "All these steps show that some staff time is required to manage the capture, storage, and distribution of digital pathology images."

Lab Informatics

Spate of Lab Informatics Deals Signals Greater Investor Interest

Halfpenny, Data Innovations, and MAS agree to sell or bring in new investors

DURING OCTOBER, three laboratory informatics companies were acquired or obtained new capital funding. It is an indication of the growing importance that laboratory informatics will play as healthcare moves toward the goal of the universal patient health record (EHR).

The first of the three transactions came on October 7. **Halfpenny Technologies, Inc.**, of Blue Bell, Pennsylvania, disclosed that it had secured $2.6 million in private venture capital. The money was provided by **Osage Venture Partners**, **Milestone Venture Partners**, and **LORE Associates**.

Halfpenny is known for its expertise in providing "clinical data integration solutions" that connect hospital labs and clinical laboratories with office-based physicians, health information exchanges (HIEs), and managed care plans. The company reports that it "has connected EMR systems in 1,500 practices to hospitals and labs" and "has successfully worked with EMR systems from more than 100 different vendors."

Data Innovations Is Sold

The next laboratory informatics transaction was announced on October 12. **Battery Ventures** purchased 100% of Data Innovations, Inc., based in Burlington, Vermont. Data Innovations is one of the larger companies offering middleware solutions to clinical labs, blood banks, and *in vitro* diagnostics (IVD) manufacturers.

As part of the acquisition, Mike Epplen will become the new CEO at Data Innovations. Epplen most recently held executive positions at **Lawson Software** and **Healthvision** (which was acquired by Lawson earlier in 2010).

Data Innovations says that it has 40 industry business partnerships, along with 6,500 installed middleware systems in 65 countries. It has written middleware solutions for about "1,000 different instruments, automation systems, and information systems."

Roche To Acquire RAL

The third lab informatics acquistion to take place was announced on October 15. **Roche Holdings** will acquire certain assets of Charlottesville, Virgina-based **Medical Automation Systems** (MAS). The deal includes the names "RAL," "Medical Automation Systems," and "MAS," as well as all of the employees related to those products. Once the deal is closed, MAS will be renamed. Roche and MAS have been co-marketing RAL for hospital glucose testing in the U.S. for more than a decade.

It is noteworthy to have three lab informatics companies involved in major transactions over a two-week period. Demand for interconnectivity and middleware solutions remains strong. Laboratories are under pressure to interface with EMRS, as well as HIEs. It is one reason why investors are interested in these lab informatics companies. TDR

INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

Southern California's always-crazy lab testing marketplace has a new laboratory competitor. In recent months, Richard Nicholson re-entered the business by acquiring **West Pacific Medical Laboratory,** based in Santa Fe Springs, California. He is assembling a team of experienced professionals to put his new laboratory company on the path to sustained growth.

MORE ON: *Nicholson*

Nicholson is best-known for his successful leadership at Santa Ana-based **Westcliff Medical Laboratories, Inc.**, prior to its sale to a private equity group in 2006. He has a reputation for conservative managed care contracting practices. During the 1990s and into the 2000s, Westcliff grew at a constant pace and was one of the most profitable of California's independent laboratory companies. Nicholson's return via West Pacific Medical Laboratory indicates that he sees continued opportunity in Southern California's intensely-competitive market for physicians' office lab test referrals.

RBM INTRODUCES BLOOD TEST FOR SCHIZOPHRENIA

In Austin, Texas, Austin-based **Rules-Based Medicine Inc.**, announced a diagnostic assay that uses a blood specimen to aid in diagnosing schizophrenia. Called VeriPsych, the lab test incorporates "the simultaneous measurement of 51 different protein and hormone biomarkers with an associated mathematical decision rule." Offered as a laboratory developed test (LDT), RMB says it will be used to affirm the "physician's clinical analysis."

TRANSITIONS

• **Vermillion, Inc.**, of Austin, Texas, has hired Jeffrey M. Salzman to be Corporate Director of Reimbursement. Salzman served most recently at **Ipsogen, Inc.** He has experience at **Monogram BioSciences**, **Quest Diagnostics Incorporated**, **Prudential Healthcare**, and **Humana**.

• Daniel R. Forche joined **CombiMatrix Corporation** of Irvine, California, to be its new Senior Vice President of Sales and Marketing. Forche was most recently at **Agendia, Inc.** He earlier worked at **US Laboratories**, **Ventana Medical Systems**, **Abbott Laboratories**, and **InSight Health Corporation**.

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...

...**General Electric's** acquisition of **Clarient, Inc.**, for $587 million. The acquisition positions GE to combine Clarient's molecular pathology technology with GE's molecular imaging technology.

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, November 15, 2010.