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"TOP TEN BIGGEST LAB STORIES FOR 2008!"
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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

A Common Future for Pathology & Radiology?

DO RADIOLOGISTS AND PATHOLOGISTS have a common future in the age of personalized medicine? That's not an idle question as new technologies help both medical specialties to better understand how molecular processes play a role in various diseases.

Oncology may prove to be the powerful force that encourages collaboration and greater clinical integration between radiology and pathology. The catalyst in the process will be the use of molecular imaging and molecular diagnostics in tandem to provide personalized medicine services to patients. While scouting speakers and topics for the upcoming *Molecular Summit on Integration of In Vivo and In Vitro Diagnostics* (*www.molecular-summit.com*), our editor heard this scenario from experts in molecular imaging and their molecular pathologist colleagues who were working together, generally in advanced research settings.

Admittedly, there are only a limited number of sites where molecular imaging and molecular diagnostics are being integrated and used in innovative ways to improve diagnosis, identify the most promising therapies, and monitor the patient's progress. Most of this is high science and definitely several years from clinical acceptance and daily use.

On the other hand, there is undeniable enthusiasm as the molecular pathologists and their imaging colleagues describe successes and share their vision. These physicians express great confidence that their approach to integrating various molecular procedures will provide physicians with powerful new tools to diagnosis patients and cure their disease.

I call your attention to these points for a simple reason. Across healthcare, pathologists are not the only physicians immersing themselves in genetic medicine and molecular technologies. Within their own specialties, radiologists, cardiologists, and other classes of physicians are doing innovative research. Add to that mix the health informaticians who are working earnestly to pour disparate sets of clinical data into sophisticated software programs, crunch that data in complex ways, then deliver clinically-relevant information to the attending physician.

Thus, it would be naive to say that lab medicine will hold the lock and key on molecular information. Across the spectrum of medicine, experts in many different fields are tinkering with genetic science and molecular technologies. That makes it likely that pathologists will be more collaborative in coming years. TDR

2008's Top Ten Lab Stories Lacked Disruptive Impact

Lab industry enjoys a time of relative quiet with few management storm clouds on horizon

CEO SUMMARY: For the first time in recent memory, a year has passed without major tumult or disruptive change in the laboratory industry. Our list of the Top Ten Most Important Stories of 2008 reflects a rather quiet year when compared to most years of this decade. However, events continue to unfold in healthcare and in the laboratory profession which require strategic responses by most clinical laboratories and pathology groups. Here's a look at this year's most interesting developments.

FOR AS EXCITING AND TUMULTUOUS as events of 2007 proved to be, the year 2008 passed by as a "yawner" for most laboratories and pathology group practices.

THE DARK REPORT'S annual list of the "Top Ten Lab Industry Stories of 2008" provides a revealing look at which breaking events and new developments were reshaping the lab industry over the course of the past 12 months.

By far the most notable story of 2008 was how the lab industry stopped the Medicare Part B Laboratory Competitive Bidding Demonstration Project dead in its tracks. The first breakthrough was a federal court ruling in favor of the plaintiff laboratories in San Diego in their lawsuit to prevent the competitive bidding demonstration project from going forward. That ruling was issued by the judge in April.

But the real prize was Congressional repeal of the legislative mandate for Medicare officials to conduct the demonstration project for the competitive bidding of Medicare Part B laboratory services. The 2008 Medicare funding bill passed by Congress in July included specific language which repealed the legislative mandate for competitive bidding of laboratory services that had been enacted earlier in the decade. *(See TDRs, April 14 and June 16, 2008.)*

No other story on the Top Ten list approaches the magnitude of importance and implications of Medicare competitive bidding repeal. However, that is a good thing because it means that, over the course of 2008, there were few events that represented disruptive or unwelcome change to the majority of laboratories and pathology group practices.

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

Ranked second on our Top Ten list is the way consumers triggered a near doubling in the volume of tests for Vitamin D deficiency over the past 12 months. This phenomenon is directly related to widespread media stories about: 1) the alarming increase in the number of people with Vitamin D deficiency; and, 2) the negative health consequences for individuals who are deficient in Vitamin D.

Consumers And Vitamin D

The explosion in Vitamin D testing demonstrates changes in several dimensions of healthcare and our society. First, the media has sustained this story at a high level of visibility because editors and reporters recognize the keen interest this topic generates among the public. Second, informed consumers are proactively listening and learning about new science which can affect their health—then using that new knowledge to proactively manage their health.

Third, health insurers rapidly responded to the regular cascade of studies about Vitamin D deficiency by keeping the issue in front of physicians and sending out information bulletins to their beneficiaries. In general, they have supported more intensive use of screening tests for Vitamin D deficiency and THE DARK REPORT has yet to hear news of payers pushing lower reimbursement onto labs because of greater utilization of Vitamin D tests by clinicians.

Government Lab Regulators

The third story on our Top Ten list for 2008 is the increased regulation of labs performing genetic testing. This has ongoing implications for the laboratory industry because government health regulators at the state and federal level took unprecedented steps during the year to assert their authority over certain aspects of genetic testing and molecular diagnostics.

For example, regulators in both New York and California sent notices to a number of Internet-based companies offering genetic tests directly to consumers. These state regulators insisted that the Internet-based genetic testing companies hold licenses to offer and perform laboratory tests. Another regulatory concern was whether a licensed physician was ordering the genetic test on behalf of the consumer. *(See TDR, July 7, 2008.)*

The FDA took steps to challenge **Laboratory Corporation of America** on its marketing of the company's OvaSure test for ovarian cancer. In response to the FDA's actions, LabCorp chose to withdraw the test while it resolves the issue. In both examples, lab regulators served notice that they intend to control activities in genetic testing and molecular diagnostics they deem contrary to existing laws and regulations.

ISO For Hospitals And Labs

Another notable development during 2008 involved ISO standards (stories number six and seven on the Top Ten list). In the hospital industry, it was big news when the **Centers for Medicare and Medicaid Services** (CMS) granted deeming status to Norway-based **Det Norske Veritas** (DNV) for hospital accreditation. DNV offers U.S. hospitals a program that combines the CMS "Conditions of Participation" with the ISO 9001 quality management system. DNV calls this program the "National Integrated Accreditation for Healthcare Organizations (NIAHO)."

In the laboratory profession, the **College of American Pathologists** initiated accreditation services to labs for ISO 15189 Medical Laboratories. Interested laboratories must maintain existing federal and state accreditation and licenses, which makes ISO 15189 accreditation an additional step. *(See TDR, March 3, 2008.)*

It is our recommendation that laboratories and pathology groups use these Top Ten Lab Industry Stories for 2008" as the basis for a strategic planning session. The list provides a good foundation to evaluate current business plans against changes in the laboratory marketplace.

TOP TEN OF 2008 no.1

Medicare Lab Competitive Bidding Stopped by Courts and by Congress

2008 LAB STORY ONE

PROBABLY NO SINGLE EVENT during 2008 had the drama of news that the Medicare Part B Laboratory Services Competitive Bidding Demonstration Project would not take place due to new Congressional legislation mandating that CMS cease implementation of the lab competitive bidding demo. *(See TDR, Monday, June 16, 2008.)*

Equally dramatic was the court victory in April, in which a federal judge ruled that CMS could not proceed with the lab competitive bidding demonstration project unfolding in San Diego, California. Several laboratories in the region had sued CMS to enjoin it from implementing what they characterized as a poorly-designed and biased competitive bidding scheme. *(See TDR, April 14, 2008.)*

Both the court decision and the Congressional repeal of authorization of the Medicare Laboratory Competitive Bidding Demonstration Project were major victories for the laboratory industry. It was widely-recognized that the demonstration program unveiled by CMS officials at a bidders' meeting in December was flawed in ways that meant it could never achieve CMS' goals for the demo even as the demo triggered disruption of efficient laboratory testing services to physicians and Medicare beneficiaries in the San Diego-Carlsbad-San Marcos metropolitan statistical area (MSA).

The importance of these two successes should not go unappreciated. It demonstrates that the laboratory industry can prevail when it educates and lobbies in effective ways.

TOP TEN OF 2008 no.2

Consumers Show How Quickly They Can Move the Lab Testing Needle

2008 LAB STORY TWO

MAYBE THE PUBLIC DIDN'T MAKE DIRECT ACCESS TESTING (DAT) a financial success, as predicted by many, including THE DARK REPORT. But the public can move the laboratory testing needle by huge amounts.

That was proven this summer when the nation's largest laboratories acknowledged that the volume of Vitamin D testing had more than doubled in the previous 12 months. **ARUP Laboratories** reported a 102% jump in Vitamin D testing. At **Mayo Medical Laboratories**, Vitamin D test volume was up by 135% in 24 months. *(See TDR, July 28, 2008.)*

This story is important for several reasons. First, it shows how quickly consumers will respond to recommendations about testing for specific health conditions. Vitamin D deficiency has been a regularly-reported story by media in this country.

Second, the sheer volume of increased testing for a condition like Vitamin D deficiency has significant financial consequences. For payers, it is an unplanned expense. For laboratories, it is the source of substantial additional revenue—but only if payers maintain reimbursement at an adequate level.

Third, attention to Vitamin D deficiency during the past two years shows how speedily a new clinical guideline can become accepted, particularly when it is something that is easy for consumers to understand.

TOP TEN OF 2008 no.3

State and Federal Regulators Act To Curb Genetic Testing Activities

2008 LAB STORY THREE

DURING 2008, STATE AND FEDERAL REGULATORS TOOK UNPRECEDENTED ACTIONS to declare their right and intent to regulate genetic and molecular testing.

At the state level, regulators in New York and California served notices to a host of companies offering genetic testing directly to consumers. New York targeted 31 companies and California sent letters to 13 firms.

State regulators wanted these companies to have required licenses and certifications under appropriate state and federal laws. California regulators also demanded proof that these 13 Internet companies were only performing tests ordered by physicians, as required by California state laws. *(See TDR, July 7, 2008.)*

It was a similar story at the **Food and Drug Administration** (FDA). Late in the year, FDA officials sent two letters to **Laboratory Corporation of America** regarding the marketing its Ovasure test for ovarian cancer. LabCorp decided to pull the Ovasure test from the marketplace as it worked to respond to the FDA's concerns. *(See TDR, October 20, 2008.)*

Collectively, these actions to regulate genetic testing by the FDA and lab regulators in New York and California are an umistakeable sign that officials intend to scrutinize, challenge, and control how genetic tests are brought to market and offered to both physicians and patients. More restrictive regulatory actions are likely in the future.

TOP TEN OF 2008 no.4

Prime Time For Rapid Molecular Tests of Infectious Diseases

2008 LAB STORY FOUR

IT'S BEEN OFT-PREDICTED that genetic and molecular testing will give labs powerful new tools for detecting disease and guiding therapy. That was certainly proven during 2008, a year when rapid molecular testing for infectious diseases contributed to remarkable improvements in patient outcomes.

At **Washington Hospital Center** in Washington, DC, use of the **AdvanDx** PNA FISH test—combined with an important change in how the lab reported results from this rapid molecular test—enabled the hospital to achieve an overall 53% reduction in deaths associated with *Staphylococcus aureus* bloodstream infections and an 82% reduction in mortality of intensive care patients. *(See TDR, July 28, 2008.)*

At **William Beaumont Hospital** in Royal Oak, Michigan, the lab launched clinical use of **Luminex Corporation's** xTag Respiratory Viral Panel. The noninvasive test screens for 12 viruses and viral subtypes that are responsible for 85% of respiratory viral infections.

Beaumont is using this panel to screen patients arriving at the emergency department with severe respiratory disorders, as well as other settings within the hospital. The rapid molecular assay delivers an answer in eight hours. *(See TDR, January 21, 2008.)*

Collectively, rapid molecular tests such as the two described above are actively changing the face of laboratory medicine by allowing labs to give faster and more accurate answers to clinicians.

TOP TEN OF 2008 no.5

Digital Pathology Systems: Coming Soon to a Laboratory Near You!

2008 LAB STORY FIVE

AFTER YEARS OF LAGGING THE RADIOLOGY PROFESSION IN DIGITAL IMAGING, the pathology profession is making swift strides toward use of fully-digital pathology systems in daily practice.

The signs were everywhere during 2008. Both **Aperio Technologies, Inc.**, and **BioImagene, Inc.**, reported accelerating sales of their digital pathology systems to pathology groups and laboratories here and abroad.

On June 5, 2008, **GE Healthcare** and the **University of Pittsburgh Medical Center** (UPMC) announced a joint venture to develop a digital pathology system capable of supporting primary diagnosis. Executives at the newly-formed **Omnyx, LLC**, believe the annual market for digital pathology systems worldwide may be as much as $2 billion. *(See TDR, June 16, 2008.)*

In this country, the ideal of a pathologist making a primary diagnosis from a digital image on a computer screen will require products that have been cleared for market by the **Food and Drug Administration** (FDA). There is progress on this goal. During 2008, for example, Aperio gained FDA approval for two specific clinical uses of its digital pathology system.

Of course, the entry of GE Healthcare into the digital pathology systems marketplace was an exciting development. It is powerful evidence that technology is ready to serve the growing demand by pathologists for digital solutions.

TOP TEN OF 2008 no.6

"System of Prevention" Management Gains Wider Acceptance in Healthcare

2008 LAB STORY SIX

DURING 2008, "SYSTEM OF PREVENTION" MANAGEMENT SYSTEMS made important inroads into both the American healthcare system and the clinical lab industry.

In September, the **Centers for Medicare and Medicaid Services** (CMS) announced that **Det Norske Veritas** (DNV) had been approved to be the nation's first new hospital accreditation program in 40 years. What made this decision particularly significant is the fact that DNV's hospital accreditation program incorporates the CMS "Conditions of Participation" with the ISO 9001 quality management system. *(See Dark Daily, October 15, 2008.)*

Earlier in 2008, the **College of American Pathologists** (CAP) had launched a new laboratory accreditation service for ISO 15189 Medical Laboratories. *(See TDR, March 3, 2008.)*

Both events show that healthcare in the United States is solidly on the path to adoption of W. Edwards Deming-based management philosophies. Health policy makers are recognizing how the same manufacturing methods used to deliver high quality–low cost electronics and similar high-tech products can also be used in hospitals and clinical laboratories to improve patient outcomes, reduce medical errors, and control costs.

Labs and pathology groups would be well-served to establish their own quality management programs. Adopting Lean and Six Sigma methods offer an effective starting point.

TOP TEN OF 2008 no.7

It's ISO 15189 for 2008 as U.S. Labs Can Now Pursue this QMS Accreditation

2008 LAB STORY SEVEN

QUALITY MANAGEMENT SYSTEMS (QMS) in clinical laboratory operations came of age in 2008 with the arrival of ISO 15189: Medical Laboratories.

The year began with the **College of American Pathologists** (CAP) announcing its accreditation program for ISO 15189. *(See TDR, March 3, 2008.)* At least three American laboratories decided to pursue accreditation.

The year ended with two of those laboratories having completed all steps for ISO 15189 accreditation and awaiting news that accreditation had been granted. They are **Piedmont Medical Laboratory** of Winchester, Virginia, and **Avera McKennan Laboratories** of Sioux Falls, South Dakota. *(See TDR, September 8, 2008.)*

Clients and regular readers of THE DARK REPORT know that ISO 15189 is gaining acceptance in many countries across the globe as a standard for laboratory accreditation and reimbursement. That is not the case in the United States and several other developed countries, where prior government accreditation requirements were in place for decades before ISO 15189 first appeared in 2003.

THE DARK REPORT believes that market forces will encourage more laboratories to implement some type of quality management system like ISO 15189. It is a standard recognized by corporations purchasing healthcare. It is also a standard recognized by patients who work in companies accredited as ISO-compliant in their own industry.

TOP TEN OF 2008 no.8

Feds Announce a Date for ICD-10, Providers Face Up to the Inevitable

2008 LAB STORY EIGHT

BECAUSE OF MEDICARE MANDATES regarding ICD-9 diagnosis codes on laboratory testing claims, the financial fortunes of clinical laboratories in the United States are inextricably linked to the diagnosis codes physicians provide when submitting laboratory test requisitions to the Medicare program.

Thus, earlier this summer, when federal officials published a proposed implementation date of October 1, 2011, for use of ICD-10 diagnosis codes, it immediately created a new management challenge for the nation's laboratories. Not only must laboratories prepare their own internal systems to accommodate ICD-10 coding requirements, but they must also work interactively with their referring physicians to ensure that laboratory test requisitions are submitted with the proper ICD-10 codes. That's because, whenever use of ICD-10 codes becomes mandatory, Medicare claims submitted after that date without an accurate and appropriate ICD-10 code will be rejected. *(See TDR, October 20, 2008.)*

Thus, laboratories will have double the costs to implement ICD-10 compared to physician groups or hospitals. A delay in ICD-10 implementation is unlikely, since ICD-10 codes have used by many developed countries around the world since 1992. That is one reason why the United States is not expected to allow further lengthy delays in the implementation of ICD-10 codes.

TOP TEN OF 2008 no.9

Cracks in the Lab Service Facade Reveal Underfunding Consequences

2008 LAB STORY NINE

IN EVERY DEVELOPED NATION ACROSS THE GLOBE, laboratory medicine faces a serious threat from the long-term consequences of underfunding and understaffing. Events in Canada during 2008 revealed visible cracks in the quality foundation of laboratory medicine.

Hospital laboratories in Canada were described as "unraveling at the seams" in an opinion piece published in the *Canadian Medical Association Journal* (CMAJ) in June. Co-author Jagdish Butany, MBBS, MS, President of the **Canadian Association of Pathologists** (CAP), wrote that labs in his country faced a "host of problems." Familiar to most laboratory professionals, these problems included the need to deal with increasingly complex and expensive medical tests, growing demands for faster results, and a critical shortage of pathologists and lab workers.

In recent years, failures by certain labs and individual pathologists to provide accurate results made headlines in Canada. Inadequate funding for lab testing services is frequently mentioned as a contributing cause.

In New Zealand, an absolute shortage of pathologists means positions go unfilled. Lack of funding for medical education is a major factor. Canada and New Zealand may be first to see inadequacies in lab testing services due to underfunding, but experts believe lab deficiencies in other developed countries will become visible in the next few years.

TOP TEN OF 2008 no.10

2008—Not a Year for Big Lab Deals As Relative Calm Rules Lab Market

2008 LAB STORY TEN

SOMETIMES A BIG STORY IS THE FACT that something didn't happen! When it comes to laboratory merger and acquistion activity, that is certainly true of 2008. Relatively few lab M&A deals happened during the year, changing a trend that stretches back more than two decades in the laboratory industry.

Yes, there were modest-sized laboratory acquisitions. For example, **Sonic Healthcare** bought **Clinical Laboratories of Hawaii** for about $121 million. **Laboratory Corporation of America** bought the outreach business of **Stanford University** this summer. Deliberately avoiding the public spotlight, **Aurora Diagnostics** discreetly purchased a handful of anatomic pathology group practices over the course of this year.

But no blockbuster laboratory deals emerged in 2008. **Bostwick Laboratories**, which had filed preliminary documents for an initial public offering (IPO), chose not to proceed. There were no deals in 2008 comparable to **Quest Diagnostic Incorporated's** takeover of **Ameripath, Inc.** in 2007 for a price of $2 billion.

Lack of truly disruptive dealmaking in the laboratory industry meant that 2008 was one of the quietest years since the mid-1980s. It is too early to declare this a multi-year trend, however. That's because dealmaking in molecular testing and *in vitro* diagnostics remains relatively vigorous, with Wall Street generally supporting strong values for companies involved in molecular testing. TDR

CEO Summary: At the upcoming Molecular Summit in Philadelphia on February 10-11, 2009, pathologists, molecular imaging experts, and informaticians will share the latest developments on the integration of* in vivo *(imaging) and* in vitro *(pathology) diagnostics. A major theme will be discussion about multi-modality diagnostics and how this new discipline—driven by advances in genetics and personalized medicine—will reshape laboratory medicine as it is practiced today.

Systems biology shifts thinking toward multi-specialty approach

Multi-Modality Diagnosis Heading for Lab Medicine

By Robert L. Michel

THERE'S A PHRASE gaining new currency in the clinical community. It is "multi-modality diagnosis" and it is gaining wider use in radiology as a way to describe imaging procedures that might involve several different technologies, such as MRI, CT, PET, and fluorescent imaging, to name a few.

However, researchers and physicians working interactively with specialists in nuclear imaging and radiology are increasingly using this term to describe any diagnostic process that incorporates a specific combination of data inputs from different scientific disciplines to produce the diagnosis.

Here is where multi-modality diagnostics intersects with laboratory medicine. In research settings across this nation, pathologists and laboratory scientists are beginning to engage with other disciplines to develop, for specific diseases and conditions, appropriate diagnostic pathways that integrate multiple relevant sources of clinical information.

Two factors are propelling this development forward. One involves the ongoing and rapid advances in genetic knowledge. The second is the recent development of a new generation of sophisticated health informatics platforms that can pull together and assess traditionally disparate sources of clinical data.

In particular, genetic medicine's use of multi-modality diagnostics will have an important consequence for pathologists and clinical laboratory professionals. Among other things, it will help tear down the isolationist attributes of laboratory medicine that have marked the specialty for decades.

Instead, during the genetic age, laboratory medicine is fated to become a highly-collaborative specialty. Laboratory professionals will interact regularly and daily as part of the patient's essential care team. This outcome will be a natural consequence of personalized medicine. It also opens the door for laboratory professionals to contribute tremendous value to patients, referring physicians, and the healthcare system.

First-mover pathologists and radiologists in this drive toward multi-modality diagnostics will be speaking at the upcoming *Molecular Summit on the Integration of In Vivo and In Vitro Diagnostics*. The conference will take place in Philadelphia on February 10-11, 2009 and is produced by THE DARK REPORT. (*www.molecular-summit.com.*)

Here is an example of how molecular imaging pioneers are bringing other disciplines, including pathology, into their clinical studies. Ralph Weissleder, M.D., Ph.D., is Professor of Radiology at **Harvard Medical School**, and Director of the Center for Molecular Imaging Research at **Massachusetts General Hospital** in Boston, Massachusetts.

Weissleder has stated that "In cancer detection, subcentimeter cancer metastases that are missed by conventional, anatomically-based imaging methods may be detected in patients by molecular imaging methods. Together with other biomarkers and emerging molecular tools (e.g., DNA screening, tissue proteomic and metabolomic analysis, serum markers), this information soon may be used for screening, diagnosis, detection of recurrence, and treatment assessment."

Weissleder's team is actively integrating *in vivo* and *in vitro* techniques to achieve these goals. At the upcoming *Molecular Summit*, Weissleder's colleague, Mukesh G. Harisinghani, M.D., Assistant Radiologist, Department of Abdominal Imaging & Intervention at Massachusetts General Hospital, will discuss the team's efforts to integrate multiple modalities to realize the clinical capabilities described above.

Molecular Intersection

THE DARK REPORT'S interest in this intersection of molecular pathology and molecular imaging began during its analysis of why **Siemens AG**—one of the world's leaders in imaging and radiology—had spent $14.1 billion in 2005 and 2006 to acquire **Diagnostics Products Corporation**, **Bayer Diagnostics**, and **Dade Behring Corporation** and become the world's second largest *in vitro* diagnostics (IVD) manufacturer.

Even as these events were unfolding, imaging giant **GE Healthcare** was making its own inroads into IVD, first with an aborted $8.3 billion agreement to buy **Abbott Diagnostics**, then earlier this year with the creation of a joint venture with **University of Pittsburgh Medical Center** (UPMC) to create and market a digital pathology system.

In Vivo/In Vitro Integration

As clients and regular readers of THE DARK REPORT recall, at the time of these corporate transactions, Siemens and GE each articulated a vision of more sophisticated diagnosis and patient care that would require the integration of molecular imaging and molecular diagnostics. Siemens further stressed the importance of adding informatics to its integration strategy and described its vision of pre-symptomatic diagnosis.

There is no better way to learn about a trend like the integration of *in vivo* and *in vitro* diagnostics than to seek out the pioneers and innovators and invite them all to come together at the same time and conduct sessions on their work. That was the genesis of the *Molecular Summit*. It took place in Philadelphia last February and was an immediate success, with 225 attendees. Fifteen different health publications sent editors and reporters to cover the event!

Trend Is Just Beginning

As pathologists and radiologists listened to the innovators in molecular imaging and molecular diagnostics last February, it was clear to both groups of specialists that integration of *in vivo* and *in vitro* was already under way—even if only at a limited number of sites across the country.

After speaking at the event, Jared Schwartz, M.D., Ph.D., wrote in his *CAP Today* President's Letter column "Returning from the Molecular Summit in Philadelphia on Feb. 6, I had to tip my hat to whoever named the meeting. They captured it perfectly. Publishers of THE DARK REPORT presented the Molecular Summit as an opportunity for professionals in pathology and radiology to learn firsthand from physicians, scientists, and industry leaders about the integration of imaging and diagnostics and the advanced uses of molecular technologies ...an intensive meeting that brings together so many of those working on the cutting edge..."

Schwartz accurately described the remarkable clinical insights tumbling out of these innovative efforts to integrate *in vivo* and *in vitro* diagnostics at the first *Molecular Summit*. But there is more to the story that is particularly relevant to pathologists. It is based on concepts that can be described as "static diagnostics" and "dynamic diagnostics."

Conceptually, anatomic pathology is a process of "static" analysis. Patient specimens used in pathology represent a specific moment in time for that patient.

Different State-Of-Practice

That makes the current state-of-practice in pathology different from the new capabilities available in imaging and radiology. New imaging technologies permit radiologists to watch the patient in a "dynamic" fashion. For example, an imaging expert can see how a tumor changes from one moment to the next.

The metaphors of "static" and "dynamic" help in understanding an emerging trend which has the potential to radically reshape surgical pathology, as well as all of laboratory medicine as it has been traditionally defined. In the conceptual sense used above, *in vitro* testing has always provided information about the patient's condition at the moment the specimen was collected.

From this traditional use of "static" *in vitro* diagnostics, most new molecular assays and genetic testing function within that tradition. That is true because the molecular specimen is harvested at a specific point in time and the diagnostic information gleaned from that specimen is understood to be based on that moment in time.

At UCLA, PET Inventor Michael Phelps, Ph.D. and Pathology Dept. have *In Vivo-In Vitro* Collaboration

AT UCLA, THE RADIOLOGY AND PATHOLOGY DEPARTMENTS are collaborating on integrated clinical services which combine *in vivo* and *in vitro* molecular technologies.

Michael E. Phelps, Ph.D., Chair of UCLA's Department of Molecular and Medical Pharmacology at UCLA and inventor of PET, is incorporating systems biology into this effort. Phelp was profiled in *Medical Solutions*, which wrote that:

Phelps views biology and the human body from a systems perspective, looking at molecular pathways in normal tissues as electronic integrated circuits, and the process of diseases as a malfunction in those circuits that can be fixed.

"If you think about a systems biology view of disease, you have to begin thinking about how the body is organized into an integrated function in the cell and the networks of cells," explains Phelps. "You have to think about how disease can reprogram those circuits to gain and lose functions and do harm to us in a different configuration in the circuit.

"People in the field of systems biology don't believe in the old concept of what breast cancer is, or prostate cancer, or Alzheimer's disease," he continued. "They believe that cells are being progressively reprogrammed into different configurations of cell circuits and intercellular networks throughout the developmental course of disease to gain and lose functions that do harm to the organ systems of the body and we must understand this so that we can deal with it effectively and therapeutically.

"All of that begins with molecular diagnostics, whether it's in vitro *in cells and blood, or* in vivo *with molecular imaging, to identify the critical proteins that consolidate specific biological processes of disease that occur in the reprogramming process. Those are the therapeutic targets; we need to either push them or to drive them back to normal or to terminate them," concluded Phelps.* [Underline by TDR.]

At UCLA, the Department of Pathology and Laboratory Medicine is in active collaboration with Dr. Phelps and his colleagues in molecular imaging and pharmacology. They are developing clinical approaches which integrate molecular imaging and molecular diagnostics. At the upcoming Molecular Summit, Jonathan Braun, M.D., Ph.D., Chair of Pathology and Laboratory Medicine at UCLA, will describe the work unfolding in prostate cancer and glioblastomas where PET-based biological probes, used in concert with molecular diagnostics, are helping physicians stratify patients with these diseases. It is an early example of integrating *in vivo* and *in vitro* molecular methods to advance patient care.

Here is where the evolution in pathology and the evolution in radiology and imaging begin to diverge. Traditionally, images collected by the radiologist also showed the patient's status as of the moment in time when the image was captured. In this aspect, *in vivo* and *in vitro* were alike and were "static."

But new imaging technologies are ready to fundamentally change the specialty of radiology. Latest-generation imaging instruments now permit the radiologist to view tissue *in vivo* and watch metabolic processes actively change the tissue of interest. This supports the concept of "dynamic" analysis. These molecular imaging technologies will alter radiology in fundamentally different ways than how molecular diagnostics are expected to change anatomic pathology.

Assume, for the moment, that this description about the static nature of IVD in pathology and the dynamic nature of *in vivo* molecular imaging in radiology is correct. There is a second transformational force under way in molecular imaging which will reinforce and strengthen radiology's evolution toward a dynamic diagnostic service. This second force is the use of latest-generation imaging systems which are bi-modal.

In the past few years, imaging manufacturers have created hybrid imaging instruments which can scan the patient during a single procedure with two different imaging technologies, such as PET/CT, SPECT/CT, and MR/PET. During presentations last February, radiologists demonstrated how these instrument systems created a new capability.

Use of the term "multi-modality diagnosis," was expanded within radiology because of how these various imaging techniques were used in combination to evaluate a patient.

These hybrid imaging instruments scan the patient with two technologies during the same procedure. The resulting images correlate precisely. This permits the radiologist to toggle back and forth and see different aspects of the same tissue. This capability created new information and new diagnostic possibilities for molecular imaging experts.

As molecular imaging experts shared the insights resulting from these technologies, this created two major "aha moments!" for pathologists at the first *Molecular Summit*. One "aha" was the recognition of the dynamic view of metabolic processes that molecular imaging technologies produce. The second "aha" was recognition that multi-modal imaging was a major breakthrough for radiologists.

Use of the term "multi-modality diagnosis," has become more common within radiology because of how these various imaging techniques are used in combination to evaluate a patient. But that's not the end of this story.

Concept Of Systems Biology

The third element contributing to the evolution of molecular imaging and multi-modality diagnostics (and not yet present in anatomic pathology to the same degree), is the concept of systems biology. Once radiologists could view tissue *in vivo* and see changes to a tumor, for example, they needed to understand the metabolic processes creating these changes. Read the comment in the sidebar on page 13 by PET inventor Michael Phelps, Ph.D. of UCLA, as to why systems biology is a main driver to his research efforts.

It is this need to understand the systems biology of the processes visible in a molecular imaging procedure that motivates radiologists to reach out to other medical specialties and collaborate with them. Of course, a natural partner in these collaborations is the molecular pathologist. Tissues of interest revealed by the molecular image must be biopsied and referred to pathologist for molecular and histopathologic analysis. This is the logical reason why *in vivo* and *in vitro* integration is already occurring.

Mustn't Forget Informatics!

These collaborations must include informatics to enable the integration of *in vivo* and *in vitro* diagnostics. Multi-modality diagnostics requires physicians to assemble and evaluate clinical data from a growing number of disciplines. Also, informaticians are independently researching ways to gather disparate clinical data sets, evaluate these data with sophisticated software, then produce an answer that the clinician can use to diagnose the patient, identify the most promising therapies, and monitor the patient's progress.

One example of this multi-modal, integrated informatics approach is occurring at **Rutgers University**. At the upcoming *Molecular Summit,* Anant Madabhushi, Ph.D., Assistant Professor and Director at the Rutgers Laboratory for Computational Imaging and Bioinformatics (LCIB), will discuss this topic. He describes his team's work as "with the advent of multi-modal, multi-parametric high resolution radiological imaging providing anatomical, biochemical, and physiological information, it has become increasingly important to identify the potential value of this information in the pre-operative or pre-therapeutic cancer population."

Machine-Learning Methods

At his laboratory, Madabhushi is focused on "developing image, spectral analysis and machine-learning methods for efficient analysis and correlation of disease signatures across multiple scales and modalities—from gene expression to histopathology to radiology, with an emphasis on prostate cancer and more recently breast cancer. Our systems approach for quantitatively analyzing multi-functional, multi-scale, multi-modal data in an integrated fashion will be extremely important in diagnostic, theranostic (predicting response to therapy), and prognostic settings."

All of these examples demonstrate that real and powerful forces in support of multi-modality diagnostics are at work in the healthcare system today. For the reasons described above, molecular imaging and radiology seem to be the most active specialty in this developing field. But a number of innovative pathologists are equally involved in expanding the boundaries and capabilities of multi-modality diagnostics.

Collaborating On A Case

For example, many pathologists are watching how neuropathologists and neuroradiologists increasingly want to see each other's images before each signs out their report on the same patient. This is also happening with bone pathologists and orthopedic oncologists. At *Molecular Summit*, there will be a case study from the **University of Kansas** where a radiologist and a pathologist are jointly looking at microcalcifications in breast cancers. These physicians report that the collaboration has not much changed the diagnosis of these patients, but, in surprisingly effective new ways, it is changing how the patients are managed.

One reason that multi-modality diagnostics has not received more attention and discussion among pathologists and the laboratory industry is that much of the current impetus behind this developing discipline is coming from outside laboratory medicine. In fact, THE DARK REPORT may be the first laboratory publication to describe multi-modality diagnostics in this fashion.

Watch The First-Mover Labs

It is too soon to predict the specific ways in which genetic medicine, multi-modality diagnostics, and the integration of *in vivo* and *in vitro* diagnostics will alter and reshape anatomic pathology as we know it today. That will take more study and observation of those clinical sites where radiologists, pathologists, and informaticians are working together to create an integrated diagnostic pathway for specific cancers and other diseases.

In the meantime, observations and comments on this subject are welcome. THE DARK REPORT is also interested in news and information about laboratories and pathology group practices which are actively involved in efforts to integrate molecular diagnostics with molecular imaging. TDR

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Marketplace Update

LabCorp Talks to Its Clients About Service Enhancements

CEO David King invites clients to respond directly to him with ideas and suggestions

BOTH NATIONAL LABORATORIES now face a future where growth is not likely to come from a steady stream of sizeable laboratory acquisitions. That makes service enhancements a more important way to protect market share and build client loyalty.

At **Laboratory Corporation of America**, this strategy can be seen in a letter the company recently distributed to its clients. Dated October 28, 2008, it was addressed "Dear Valued Client" and was signed by LabCorp CEO David King.

The letter described four specific service improvements that would be of benefit to the client physician. First was an invitation to visit "LabCorp's new Web site", which includes such new functions as expanded test search capabilities, a patient health library, and additional "features and time-saving tools."

The second new service improvement is designed to address the problem of insufficent draw quantity. LabCorp has created AccuDraw. This is a computer decision support system for its phlebotomists. AccuDraw evaluates each test request for individual patients, then guides the phlebotomist through the tube types and volume needed, order of draw, and instructions for special handling.

The third service improvement touted in King's letter is the new capability to do a "HPV high risk reflex" test when the original specimen won't yield "sufficient residual specimen volume after the Pap preparation to perform the HPV test." The benefit of this new assay is that it reduces the number of times that a patient needs to be called back to recollect an adequate specimen for the additional testing.

Specimen Tracking System

Fourth service improvement described in the LabCorp letter is the announcement that the company has purchased and implemented "a new, state-of-the art specimen tracking system—originally created by UPS." It says it expects "improvements in turnaround time and a move to real-time specimen tracking with built-in alerts for misplaced specimens."

CEO David King ends the letter by inviting clients to email or call him with ideas or suggestions. He provides a phone number and an email address that can be used by clients.

For independent labs and hospital lab outreach programs, this letter is a reminder that the service status quo in the marketplace is not likely to remain constant. LabCorp hopes these types of service enhancements will raise the competitive bar in its favor. Likewise, **Quest Diagnostics Incorporated** is implementing its own operational improvements to raise its service levels.

These are reasons why competing laboratories should have their own strategies to improve their services. What is acceptable service to a client physician today may not be good enough tomorrow. TDR

Momentum Continues for Digital Pathology

FDA clears reading of Aperio's digital progesterone receptor slides on computer monitor

CEO SUMMARY: Last month, digital imaging in pathology gained additional momentum with the latest FDA clearance. Aperio Technologies, Inc., now has FDA clearance to market its slide scanning system for reading digital progesterone receptor (PR) slides on a computer monitor. Aperio plans to file an application next year with the FDA for clearance to use its digital pathology imaging system for the reading of digital H&E breast tissue slides on a computer monitor.

USE OF DIGITAL SLIDE IMAGES for primary diagnosis in anatomic pathology took another step closer to wider market acceptance on November 18 with news that the **Food and Drug Administration** had cleared reading of digital Progesterone Receptor (PR) slides from a computer monitor using the digital pathology system of **Aperio Technologies, Inc.**, of Vista, California.

This endorsement is Aperio's second FDA clearance for diagnoses using digital slides. Last December, the FDA cleared Aperio's system to read digital HER2 slides from a computer monitor. The company (*www.aperio.com*) has an installed base of more than 450 systems in 28 countries. Lab users of this system include top-ranked hospitals, academic medical centers, and reference laboratories, along with a number of major pharmaceutical companies.

Equivalent to Glass Slides

"Our FDA clearances for diagnosing digital HER2 and PR immunohistochemistry (IHC) slides on a computer monitor demonstrate that our digital pathology system is equivalent to diagnosing glass IHC slides under a microscope," explained Aperio CEO Dirk Soenksen. "The system aids pathologists in detecting and measuring PR or HER2 by manual examination of the digital slide on a computer monitor.

"The specimen viewed is a formalin-fixed, paraffin-embedded normal and neoplastic tissue that has been immunohistochemically stained," noted Soenksen. "The image of that specimen is captured digitally and presented to the pathologist on the computer monitor."

Aperio's next goal is to pursue FDA clearance for diagnosing digital H&E slides. "We expect to submit an application to the FDA for clearance to market our system for the diagnosis of digital H&E breast cancer slides next year," predicted Soenksen.

Aperio believes that demand within the United States for digital pathology systems will increase dramatically when Aperio, and other manufacturers, can promote the use of digital slides for the most common types of pathology diagnoses. That belief is why the company is pursuing a series of FDA clearances, each of which will permit a pathologist to diagnose specimens digitized by an FDA-cleared system on a computer monitor.

In January, 2008, Aperio gained its first FDA clearance for the diagnosis of HER2 digital slide images from a computer monitor. Last month came Aperio's second FDA clearance, for use of its digital pathology system for the diagnosis of PR digital slide images from a computer monitor. Next year, in 2009, Aperio wants to file to obtain an FDA clearance that will allow its system to be used to diagnose H&E digital slides from a computer monitor.

While Aperio is the first and only company to receive FDA clearance for a system that can be used for making diagnoses from digital slides for clinical use in pathology, these FDA clearances are important to the wider pathology community. Each clearance establishes a precedent that makes it easier for other companies to submit digital pathology systems to the FDA and obtain clearance to market those systems for clinical applications.

From that perspective, Aperio's FDA clearances are opening a path for other companies to follow as they seek regulatory approval for their digital pathology systems. In turn, easier regulatory clearances will encourage research centers and other companies to develop and introduce a greater number of digital pathology products.

"The challenge for manufacturers is that digital pathology systems cannot be marketed for specific clinical applications without FDA approval," noted Soenksen. "Having FDA clearances makes it possible for manufacturers to legally promote the newly-cleared clinical uses of a digital pathology system.

Looking Five Years Ahead

"If you look forward five years, everyone marketing digital pathology solutions will have these clearances," he added. "That's what happened in radiology. Some pioneering radiology imaging companies obtained the first required FDA clearances and other companies followed.

"Also, as the FDA clears specific applications of digital pathology systems for diagnosis from a digital slide image on a computer monitor, more pathologists may consider other ways in which they could use this technology for what is called an 'off label use'," he added.

"Pathologists may use digital pathology systems any way they like, so long as their laboratory properly validates that use under CLIA guidelines," said Soenksen. "That is why FDA clearances for our HER2 and PR diagnosis applications broaden the comfort zone for existing pathology customers to use digital pathology system 'off label'—that is, for applications that are similar to those that have been cleared. Should we obtain an FDA clearance for diagnosis of digital H&E breast tissue slides, it is conceivable that pathologists would be comfortable self-validating digital pathology for applications such as lung and prostate cancer.

Acceptance Outside U.S.

"In fact, outside the United States, there is broader acceptance for pathologists to use digital pathology systems for clinical applications," Soenksen said. "In Canada, pathologists report their use of this technology for remote diagnosis. In Toronto, for example, it allows pathologists to consult on cases at a hospital 400 miles away." *(See TDR, July 7, 2008.)*

"The question is no longer whether digital technology is good enough for diagnosis," he said. "Already, manufacturers' efforts to obtain regulatory clearances lag behind the acceptance and use of digital pathology for diagnosis by respected labs in many countries across the globe. The question now is how long will it be until, within the United States, there is wider self-validated use of this technology for other areas of pathology beyond PR and HER2 testing for breast cancer."

These FDA clearances are one reason why pathologists and practice administrators should keep a watchful eye on the digital pathology imaging marketplace. Digital pathology is advancing swiftly. TDR

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INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

Having grown to over $1 billion in revenue, **Inverness Medical Innovations, Inc.** of Waltham, Massachusetts, is newest of the *in vitro* diagnostics (IVD) companies to achieve size and scale. One of its more interesting products is an in-home system that allows warfarin patients to test themselves and produce PT/INR results. Inverness' INRatio2 PT/INR Monitoring System has FDA clearance. Inverness reports that some payers have agreed to reimburse for this testing system when a physician issues a prescription.

MORE ON: Inverness

In-home PT/INR testing is booming at Inverness. Recently Chairman, President, and CEO, Ron Zwanziger told investors that "Referral of patients by prescription from physicians has increased from an average of 700 per month in the second half of 2007, to over 1,800 per month on average for Q3 of 2008." In-home patient self-testing for PT/INR shows how advances in diagnostic technology continue to give physicians and payers new options for performing laboratory tests.

POCT TROPONIN STUDY REPORTS GOOD TAT RESULTS

While on the subject of point-of-care testing (POCT), a study published this summer in the *Annals of Emergency Medicine* reported favorably on the ability of POCT troponin to reduce turnaround times in the emergency department (ED) when used for patients with chest pain or acute coronary syndrome (ACS). The study was the first randomized controlled clinical trial to evaluate emergency department length of stay when troponin POCT was used. It involved 2,000 patients.

ADD TO: POC Testing

The study was led by Richard Ryan, M.D., Vice Chairman, Department of Emergency Medicine at the **University of Cincinnati College** of Medicine. EDs at **The Jewish Hospital** in Cincinnati, **William Beaumont Hospitals** in Detroit, the **University of Pennsylvania**, in Philadelphia, and **Stanford University** in Palo Alto, California, participated in the study. **Abbott Laboratories'** i-Stat instrument was used in the study, which determined that POCT troponin results took less than the 60-minute recommended turnaround time in 98% of the episodes, compared to 53% for results from the core laboratory. For the 30-minute turnaround time, POCT results met that goal 87% percent of the time, versus just 3% for troponin results from the core lab.

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DARK DAILY UPDATE

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...the "Top Ten Germiest Jobs" as identified by a microbiologist from the **University of Arizona**. Lab scientists are fifth germiest on the list, behind doctors/nurses and ahead of police officers.

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That's all the insider intelligence for this report. Look for the next briefing on Monday, December 22, 2008.