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From the Desk of R. Lewis Dark...

THE DARK REPORT

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

Restricted information, see page 2

Commentary & Opinion by...

R. Lewis Dark

Founder & Publisher

Labs Poised to Add Value to Docs and Patients

CAREFULLY READ OUR COVERAGE AND ANALYSIS about cytochrome P450 (CYP450) testing on pages 2-9. CYP450 testing is likely to be one of the most important developments in laboratory medicine in the past two decades.

I say that for two reasons. First, test panels designed to detect multiple polymorphisms in cytochrome P450 will allow physicians to determine, in advance and with increasing accuracy, how a specific patient will respond to a specific drug. Second, CYP450 testing will be appropriate prior to issuing prescriptions that cover 25% or more of the existing formulary.

CYP450 testing promises two positive outcomes for the healthcare system. "Trial and error" prescribing will be greatly reduced, since physicians will know ahead of time whether the patient will get therapeutic benefit from a specific drug. The number of adverse drug reactions (ADRs) will decline, since the physician was able to determine, in advance, that the patient was a no-metabolizer, slow-metabolizer, or ultra-fast-metabolizer.

With 2.8 billion prescriptions filled each year in the United States, this positions CYP450 testing to become a high-volume test for any laboratory with a certain size and scale. Because CYP450 testing yields high clinical value, experts believe it will be appropriately reimbursed. These two reasons, taken together, are stirring excitement among certain vendors and the nation's largest laboratory companies.

I'd like to add one point to our coverage about CYP450 testing. I believe that consumers will be quick to push rapid adoption of this test by individual physicians. As the word gets out about how this test can help avoid serious, even fatal, adverse drug events, consumers will do their homework. Educated and armed with facts printed from the Internet, they will challenge their doctors and insist that these tests be ordered for themselves and their family members. This is a major development and you are among the first to understand how and why CYP450 testing has the potential to be transformational across our healthcare system.

Furthermore, this is another example of how THE DARK REPORT gives you actionable business intelligence, along with the time and knowledge needed to position your laboratory or pathology group ahead of events. Once more, THE DARK REPORT has provided you with a priceless competitive advantage over your laboratory competitors! TDR

CYP450 Testing To Have Major Clinical Impact

Analysts predict that wider clinical adoption of CYP450 testing will benefit lab industry

CEO SUMMARY: Pharmacogenomics, companion diagnostics, "personalized prescription drug therapy"–by any name, use of molecular diagnostics to guide clinicians in the prescribing and dosing of drugs is about to expand exponentially. Some experts predict that CYP450 testing alone will be a $1 billion business for labs in just a few years. Here's a look at the forces driving this new opportunity.

THERE'S A MAJOR CLINICAL AND FINANCIAL HOME RUN looming for the laboratory industry. It's testing based on cytochrome P450 (CYP450).

"We expect that the clinical lab market for companion diagnostic tests will expand substantially over the next several years," predicted Bill Bonello, Research Analyst with **Wachovia Capital Markets**. "CYP450 2D6, 2C19 and 2C9 could be the first meaningful new tests, but other tests are sure to follow.

"We believe the value of this market could be over $1 billion in the next several years," said Bonello. "Over time, we believe this market is likely to reach $3 billion."

CYP450 tests identify genetic variants that impact metabolism for 25% or more of the current drug formulary in the United States, For some time, scientists have known that variations in the CYP2D6 and CYP2C19 genes are predictive of drug metabolism. What they lacked was a way to rapidly and accurately identify these variations for large numbers of people.

Bonello believes that CYP450 tests now entering the market could be accepted by the clinical community. "There is enormous potential for physicians to determine appropriate drug therapies and dosing for a number of commonly prescribed drugs, including Warfarin, Zoloft, Prozac, Straterra, certain beta blockers, and other drugs," said Bonello.

The ability to predetermine the benefit—or potential adverse reac-

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SUBSCRIPTION TO THE DARK REPORT INTELLIGENCE SERVICE, which includes THE DARK REPORT plus timely briefings and private teleconferences, is $11.90 per week in the US, $12.50 per week in Canada, $13.65 per week elsewhere (billed semi-annually).

tion—to patients of a particular drug therapy represents just the first step in pharmacogenomics. Other tests are sure to follow. As clinicians begin to use these tests, pressure will mount for laboratories to provide these assays. It will require significant investments of capital to acquire the technology and highly-skilled staff needed to perform these tests.

In Bonello's opinion, the diagnostic assay best-positioned to ride this clinical wave is the Amplichip™ CYP450 Array offered by **Roche Molecular Systems, Inc.** This test is a microarray that utilizes the GeneChip® System 3000Dx manufactured by **Affymetrix, Inc.**

31 SNPs In A Single Assay

Using DNA extracted from a patient's blood, Roche's microarray assay searches for 31 different genetic variations—polymorphisms and mutations—in the cytochrome P450 enzymes. These polymorphisms affect the ability of a patient's liver to metabolize certain drugs, as well as the rate of metabolism. Both systems were cleared for clinical use by the **Food and Drug Administration** (FDA) on December 23, 2004.

THE DARK REPORT concurs with Bonello's assessment that microarray-based CYP450 testing has the possibility to be the next clinical and revenue-generating blockbuster in laboratory medicine. THE DARK REPORT was first to note the importance of this development. *(See TDR, January 3, 2005.)* It was also first to provide presentations on this topic to lab directors and pathologists by having Sunil Hazaray, Vice President of **Roche Molecular Systems**, address the *Executive War College* in May 2005.

In fact, Bonello will be discussing CYP450 gene testing in greater detail at the upcoming *Executive War College on Laboratory and Pathology Management* in Miami on May 3, 2006. Bonello is the first financial analyst to look at the factors which will drive clinical demand for CYP450 testing and how it will financially benefit the laboratory industry.

Labs Now Offer The Test

"Right now, only a handful of laboratories offer CYP450 testing, including **Quest Diagnostics Incorporated** and **Laboratory Corporation of America**," stated Bonello. "But we expect to see a steady expansion in the number of laboratories which offer this test. The AmpliChip test has been found to be most effective in evaluating the patient response to 15 commonly prescribed compounds. *(See sidebar on pages 5-6.)*

"Clinicians write approximately 70 million prescriptions for these therapeutic drugs every year," continued Bonello. "Based on the modest assumption of an initial new patient screening rate of 4% and a price of $400 per test, the near-term market potential is $650 million!

Reimbursement Unknown

"Reimbursement levels for this test remain unclear," he observed. "The near-term price point for this test may even be much higher than $400—perhaps as much as $1,300 per test initially."

The existing market for companion testing is relatively small and centers around HIV genotyping and HER2/neu, used in conjunction with Herceptin. "The HIV genotyping market alone went from $0 in 1997 to $175 million within three years," Bonello said. "Compared to HIV and HER2/neu, the potential clinical demand for CYP450 testing is huge.

"We estimate that Quest Diagnostics and LabCorp could each generate approximately $250 million of annual

revenue and $50 million in EBIDTA (Earnings Before Interest, Depreciation, Taxes, and Amortization) from CYP450 testing, over time," stated Bonello. "Each could capture 40% of the near-term market. In the longer term, other laboratories will likely offer competing CYP450 tests."

Three Market Factors

Bonello identifies three market factors that could affect the rate at which clinicians adopt CYP450 testing. "One, any FDA labeling requirements—such as for Warfarin and other commonly prescribed drugs—could cause expansion in the market," predicted Bonello. "Two, as other tests and drugs come into the marketplace, adoption rates would expand even further. Three, payer reimbursement rates will be a critical component impacting the adoption of new tests based on CYP450."

Despite strong, even compelling evidence in favor of widespread testing for CYP450, Bonello points out three possible barriers. "It will take some time for the clinical community to sort out the precise factors which can influence drug metabolism," he explained. "These can include age, race, liver function, co-morbidity, and nutrition.

Will Docs Be Reluctant?

"Next, in the absence of evidence-based protocols and guidelines delineating proper clinical response to genotypic information, clinicians may be reluctant to use the test," explained Bonello. "A third factor may be payer reluctance to pay for these tests.

"On the other hand," he continued, "even without clear protocols and guidelines, many clinicians may feel a moral and ethical responsibility to use CYP450 screening for two reasons. One, CYP450's ability to predict drug toxicity could trump other uncertainties. Two, physicians may be concerned about potential liability if they do not offer these predictive tests.

"With the increased focus on patient safety, the FDA may start requiring reference to pharmacogenetic testing on the labels of prescription drugs," speculated Bonello. "Currently, there are over two million adverse drug reactions and 100,000 deaths per annum in the U.S. attributable to improper drug dosing and other adverse drug reactions (ADRs). Potential FDA labeling requirements would impact a broad array of new and existing drugs."

CYP450 Research

During the past decade, numerous papers have been published in peer-reviewed medical journals about how genetic variation in cytochrome P450 affects the ability of individuals to metabolize certain drugs and gain therapeutic benefit. There is plenty of evidence and agreement within the healthcare community that CYP450 testing can help clinicians prescribe the right drug for individual patients, thus improving clinical outcomes and reducing the number of adverse drug events.

In the next briefing, THE DARK REPORT provides an analysis of the factors which support increased use of CYP450 tests prior to prescribing many drugs in the current formulary.

As Bonnello has indicated, there are powerful economic and clinical reasons why use of CYP450 tests should increase. Just one example illustrates this point. Within hospitals, there are 2.2 million adverse drug reactions (ADRs) each year in the United States and more than 100,000 deaths are attributed to these ADRs. TDR

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—By Pamela Scherer McLeod

(See sidebar on following pages.)

Looking at the Potential of CYP450 Testing to Support Prescription Ordering

Drugs: Zoloft, Toprol, Straterra, Others

Companion Diagnostic: CYP450-2D6/2C19 Genotype Currently Offered at Quest Diagnostics and LabCorp

Purpose of Test: To identify the presence of genes that produce CYP2D6/CYP2C19 enzymes, which may be linked to increased/reduced effect of drugs. CYP2D6/CYP2C19 metabolize approximately 40% of all clinically used medications, including Beta-blockers, antiarrhythmics, antidepressants, dextromethorphan, and morphine derivatives

Est. Market for CYP450 2D6/2C19 Test	Near-term	Long-term
Est. Annual New Prescriptions Of Companion Compounds	70,000,000	90,000,000
Est. Utilization Of CYP450 2D6/2C19 Screen	4.0%	40.0%
Est. Annual Number of CYP450 2D6/2C19 Screens	2,800,000	36,000,000
Est. Revenue Per Screen [a]	$400.00	$100.00
Est. CYP450 2D6/2C19 Screening Market	$1,120,000,000	$3,600,000,000
Est. Royalties	$448,000,000	$1,440,000,000
Est. CYP450 2D6/2C19 Screening Market, Net	$672,000,000	$2,160,000,000

Drugs: Warfarin, Zoloft, Azathioprine, Glipizide, Phenytoin

Companion Diagnostic: CYP450-2C9 Genotype Currently Offered at Quest Diagnostics and LabCorp

Purpose of Test: To identify the presence of genes that produce CYP2C9 enzymes, which may be linked to increased/reduced effect of drugs. CYP2C9 metabolizes approximately 5% of all clinically used medications, including anticoagulants, antidepressants, and other compounds

Estimated Market For CYP450 2C9 Test	Near-term	Long-term
Est. New Prescriptions Of Companion Compounds	30,000,000	30,000,000
Est. Utilization Of CYP450 2C9 Screen	15.0%	50.0%
Est. Annual Number of CYP450 2C9 Screens	4,500,000	15,000,000
Est. Revenue Per Screen [a]	$100.00	$100.00
Est. CYP450 2C9 Annual Screening Market	$450,000,000	$1,500,000,000

Revenue Impact of CYP450 2C9 Screening for Quest Diagnostics in 2007		
Est. % of Market	20.0%	20.0%
Est. CYP450 2C9 Revenue	$90,000,000	$300,000,000
Est. CYP450 2C9 Test EBIT Margin	20.0%	20.0%
Est. EBIT	$18,000,000	$60,000,000

[a] Estimated Reimbursement For CYP450 Screen

Source: IMS and Wachovia Capital Markets, LLC estimates.

Listed below are fifteen of the most frequently ordered prescriptions which have metabolic pathways that are highly influenced by CYP450 2D6 and 2C19 polymorphisms and mutations. In 2004, over 48 million new prescriptions were written just for five of these compounds, including Warfarin and Zoloft. Financial Analyst Bill Bonello of Wachovia Capital Markets used this list to develop projections for CYP450-based diagnostic testing in 2007. This projection is based on the rate of new prescriptions at a test price of $400 for the 2D6/2C19 screen. In 2007, the potential market is projected to be worth as much as $8.6 billion. Between 2008-2010, Bonello projects the market will grow at about $1 billion yearly, based on increased utilization by clinicians.

# NEW PRESCRIPTIONS IN 2004	
• toprol	12,151,608
Beta Blockers	
• propranolol	1,857,804
Antidepressants	
• zoloft	12,712,020
• fluoxetine	9,234,396
• fluvoxamine	448,836
• nortriptyline	1,498,572
• paroxetine	7,348,500
• venlafaxine	N/A
Antipsychotics	
• haloperidol	1,135,428
• perphenazine	162,252
Others	
• straterra	2,857,812
• prevacid	10,000,000
• nexium	9,000,000
• codeine	541,464
• tamoxifen	707,004
CUMULATIVE TOTAL	**69,655,696**

CYP450 Plays Major Role In Drug Metabolization

Potential for CYP450 testing to be done in support of tens of millions of prescriptions

CEO SUMMARY: Each year, over 100 million new prescriptions are written for two classes of drugs with metabolic pathways affected by genetic variations in cytochrome P450. There are strong clinical arguments in favor of testing individuals for these genetic mutations to determine whether they are no, slow, or ultra-fast metabolizers of these drugs, before writing the prescription.

IT'S SIMPLE TO UNDERSTAND the clinical reasons for adopting testing based on cytochrome P450 (CYP450). In the United States, adverse drug reactions (ADRs) are a major source of deaths and tens of billions of dollars in related healthcare expenses.

That's because drug efficacy and toxicity vary substantially across individuals. In today's healthcare system, drugs and doses are typically adjusted by trial and error. That means physicians use a "hit or miss" approach to identify the right drug and the right dose.

Factors Causing ADRs

Many factors may influence the effect of a drug on an individual. These factors include age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Other factors that may also have major effects on the efficacy or toxicity of a drug are inherited DNA sequence variation (polymorphisms) in genes for drug-metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways.

New and emerging pharmacogenomic tests have the capability to predict therapeutic failures in individual patients or severe adverse drug reactions. These tests evaluate genotypes for important polymorphisms that affect key drug-metabolizing enzymes, receptors, and transporters.

Such pharmacogenomic tests have the potential to help clinicians optimize the choice of drug and proper dose much earlier in the treatment cycle. These pharmacogenomic tests would position laboratory testing as a major contributor to better therapeutic outcomes, the avoidance of serious side effects, and reduced medical costs.

These are the reasons why the laboratory industry is poised to hit a major clinical home run with CYP450 and other pharmacogenomic testing. This testing has the potential to dramatically reduce many problems related to prescription drugs. Adverse drug reactions (ADRs) are a major source of poor clinical outcomes and the healthcare system is eager to find effective solutions to manage this problem.

Recently, Michael Caldwell, M.D., Ph.D., Director of Medical Research at **Marshfield Clinic** in Marshfield, Wisconsin, made a presentation to the **Food and Drug Administration** (FDA) titled "Predicting the Stable Dose of Warfarin." Dr. Caldwell quoted studies that estimate the number of adverse drug reactions for hospitalized patients to be 2.25 million per year, causing more than 106,000 deaths annually.

If these studies are accurate, ADRs are the fourth leading cause of death in the United States, ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents, and automobile deaths. Dr. Caldwell observed that there is no reliable methodology for estimating ADRs and related deaths in ambulatory settings, but that 350,000 ADRs occur in nursing homes each year.

Tens Of Billions Of Dollars

Caldwell also referenced a study that estimates the annual cost of ADRs to the United States is *$136 billion!* This exceeds the cost of cardiovascular or diabetic care in this country. Further, one out of five injuries or deaths to hospitalized patients may be the result of ADRs and a "two-fold greater mean length of stay, cost, and mortality has been reported for a hospitalized patient experiencing an ADR compared to a control group of patients without an adverse drug reaction."

These are huge numbers and explain why there is support and interest in CYP450 and similar tests. Clinicians need a way to more accurately predict how individual patients will respond to a specific drug and whether that patient may experience adverse drug reactions.

Genetic Variants

As noted in the preceding story, CYP450 tests are capable of identifying genetic variants that impact metabolism for at least 25% of all prescription drugs

Roche Sees A Market For CYP450 Testing

IN PUBLIC STATEMENTS, Roche Diagnostics has predicted sales of CYP450 testing to reach $100 million by 2008. But that is only the first phase in the market development of CYP450 testing.

Roche executives are optimistic about the long-term growth potential for such testing. In public statements, Heino von Prondzynski, CEO of Roche Diagnostics, predicted that the gene chip market worldwide may reach $8 billion to $10 billion by 2015.

Von Prondzynski believes that clinical benefits will not be the only motive to expand CYP450 testing. In general, he believes the demand for pharmacogenomic tests will be driven, in part, by litigation fears. "If a patient suffering from an adverse drug reaction learns he could have avoided it if his physician had done such a test because he is a poor metabolizer, this is something that will drive the use of the test," stated Von Prondzynski to a reporter from **Reuters**.

Because Roche is big in both pharmaceuticals and diagnostics, its confidence in the future of CYP450 testing and pharmacogenomics in general represents an important shift from the existing mindset within the pharmaceutical industry. Until now, most big pharmaceutical companies have approached pharmacogenomics with caution. The drug industry has traditionally relied on a small number of multi-billion-dollar "blockbuster drugs" to drive sales and profits. Pharmacogenomics threatens to explode that model if, in the future, drugs are tailored to small groups of patients.

That is not the belief at Roche, a company with a considerable presence in both therapeutic drugs and *in vitro* diagnostics. Von Prondzynski has stated that, by the year 2020, it is possible that, for every $2 spent on prescription drugs, pharmacogenomic testing could generate $1.

now in the formulary. That gives CYP450 testing the potential to be a blockbuster for the laboratory industry, both clinically and financially.

A look at key numbers reveals why. In 2000, there were 2.8 billion prescriptions written in the United States, which is an average of almost 10 prescriptions per person. Estimates are that about 64% of patient visits to physicians result in prescriptions and the incidence of ADRs increases exponentially once a patient is on four or more prescriptions.

Remarkable Statistics

Other remarkable statistics suggest why CYP450 testing would be of high value to patients and physicians. Within certain population subsets, there are significant polymorphisms which contribute to potentially fatal outcomes connected to specific drugs.

For example, CYP29C has a polymorphic distribution in the population. It is missing in about 1% of Caucasians. It is a primary enzyme responsible for metabolism of many non-steroidal anti-inflammatory drugs, including second generation COX-2 inhibitors. CYP450 2C9 plays a key role in metabolizing warfarin (Coumadin). Caldwell notes that "almost all inter-patient variability in warfarin levels and anticoagulant effects can be explained on the basis of CYP2C9 activity (not the differences in protein binding as thought)."

Cytochrome P450 2C19 is genetically absent in between 20% and 30% of Asians. Caldwell says "this enzyme metabolizes many anticonvulsants, diazepam (Valium), omeprazole (Prilosec), and several of the tricyclic antidepressants...Asians have a reduced clearance of diazepam compared to Caucasians."

In terms of rapid metabolization, upwards of 30% of Ethiopians in a study were determined to have multiple copies of the 2D6 gene (as many as 13 copies). In affected individuals, this causes lower blood levels of a standard dose of any drug metabolized by this enzyme. In particular, 2D6 affects standard doses of beta blockers, narcotic analgesics, and antidepressants. These individuals may need higher dosages to achieve clinical results.

Psychiatry is one of the first medical specialties to use CYP450 testing to help guide clinicians in prescribing the most effective drug for individual patients. In her presentation on molecular diagnostics and pharmacogenomics at the *Executive War College* in New Orleans last May, Gwen McMillan, Ph.D., described how psychiatrists were using CYP450 tests to eliminate "trial and error" prescribing practices and more quickly match an effective drug to the patient, while minimizing negative side affects. McMillan is the Medical Director of Clinical Toxicology and Trace Elements Laboratories at **ARUP Laboratories** in Salt Lake City, Utah and has seen a pick-up in pharmacogenomic testing by psychiatrists referring tests to her laboratory.

Financial Home Run

One fact and one statistic dramatically demonstrate the potential of CYP450 testing to be a financial home run for the laboratory industry. The fact is that CYP450 testing predicts how patients will metabolize individual drugs comprising 25% of the current formulary. The statistic is that 2.8 billion prescriptions are written each year in the United States.

By implication, this means that the laboratory industry is likely to be doing high volumes of CYP450 testing in coming years. Because of the value of this testing to the healthcare system (in outcomes improvement and cost reduction), there are reasons to be optimistic that reimbursement for these tests will be adequate. TDR

Outcomes Update

Payers Want Patients to Shop Prices at Doctors' Offices

Health insurers plan to use cell phone feeds to provide prescription drug prices to patients

PRICE SHOPPING BY PATIENTS is getting major encouragement from the nation's largest health insurance companies. But the big surprise is the proactive steps some insurers are taking to involve patients in decisions about their healthcare.

Take, for instance, a service that will let patients enter the name of a drug into the Web browser of their cell phone. They will immediately see a list of comparable drugs, ranked by cost according to the patient's insurance plan! The goal is to let the patient, while still in the presence of the physician, ask about cheaper alternative drugs.

The company offering this service is **Lumenos, Inc.**, based in Alexandria, Virginia. The company is owned by **Wellpoint Systems, Inc.**, the largest health insurance corporation in the United States.

Suggesting Care Options

Another new approach to educate consumers is to send them letters that suggest questions to ask their doctors, tests and medications that might be appropriate, or alternative approaches to care that they can discuss with their physicians. Alternatively, some health plans are using financial statements to offer suggestions about care.

To take advantage of this demand for patient education, entreprenuers have founded a company that contracts with health insurers to send these types of letters to their beneficiaries.

Based in Chevy Chase, Maryland, **Resolution Health Inc.** uses a proprietary system to analyze health plan data. It can then classify beneficiaries into clinically meaningful categories and identify opportunities to "improve the quality, safety and effectiveness of care being provided to each member."

On behalf of its client health plans, Resolution Health can then send personal health statements to individual members—and an accompanying report directly to the member's physician—that describes possibilities for improving the patient's health. These statements also suggest ways the patient could reduce his or her out-of-pocket expenses. Major health insurers, including **Blue Shield of California, Horizon Blue Cross Blue Shield of New Jersey**, and **PacifiCare**, use these services.

Making provider prices available to members is another strategy. **Aetna, Inc.** was first to do this when, for its members in Cincinnati, it began posting the prices it pays physicians on its Web site. Now **Cigna Corporation** has a similar program. It is going further, not only telling the member what the price is, but also what services should be provided and how many minutes he or she should typically spend with the doctor. TDR

Placenta Registry Stirs Unwarranted Controversy

Ob-gyns and pathologists nationally are working together to more effectively examine placentas

CEO SUMMARY: On the surface, the "exposé" published by* The Oregonian *newspaper on February 12 seemed designed to sensationalize an effort by local obstetricians, hospitals, and pathologists to do a better job of evaluating placentas taken from patients who had experienced a difficult birth as an arrangement intended to provide a defense in malpractice cases. But deeper investigation uncovers a more benign story.

On February 12, 2006, *The Oregonian* newspaper in Portland, Oregon published a story about how, from 1996 to 2003, the placentas from as many as 700 women who had difficult births were sent to a laboratory in Portland, Oregon. The placentas were examined, and the women were not told, according to *The Oregonian*.

This story directly implied that the existence of the **Cascadia Placenta Registry**, as this specialized laboratory was called, was exclusively an arrangement organized around malpractice concerns related to difficult births. The newspaper pointed out that some of the women learned about the registry only after filing a malpractice lawsuit.

Hospitals In Three States

The Oregonian also published information that the original funding to launch the Portland, Oregon-based Cascadia Placenta Registry in 1996 had come from malpractice insurers, a number of hospitals, and a malpractice attorney in the area. During the years it operated the registry accepted placentas for study from hospitals in Oregon, Washington, and California.

For pathologists and ob-gyns in the Northwest, however, the Cascadia Placenta Registry was not news. The registry was established to collect medical information that could be used to help protect doctors and hospitals if needed against a malpractice lawsuit. While it was in operation, it provided a useful and needed service not available elsewhere, according to an ob-gyn and a pathologist interviewed by THE DARK REPORT.

"Sometimes, there's a lot to be a learned from the placental material," said Robert D. Dyson, M.D., an ob-gyn with **Gateway Women's Clinic** in Portland, Oregon. "Many of the questions we have regarding births get answered with pathology reports, and the local pathologists are perfectly able to answer most of them. But if it's a difficult birth, there are sometimes subtleties involved in the pathology that we need to know about. The idea

Cascadia Placenta Registry Not the First Attempt to Identify Problems, Improve Care

PORTLAND, OREGON'S CASCADIA PLACENTA REGISTRY was not the first effort to use a placenta registry as a way to better diagnose problems and improve obstetric care.

There has been growing recognition for the need to develop more advanced knowledge of placental pathology. That's because of increased knowledge about how different diseases and conditions affect the placenta.

In recent years, the **College of American Pathologists** (CAP) has encouraged initiatives designed to advance pathologists' skills in evaluating and diagnosing placentas. These efforts have had some notable successes.

For example, one initiative was the **Arizona Placental Project**. During the time it was active and reviewing placentas, pathologists participating in this project have said that no obstetrician was successfully sued for delivery-related malpractice, in a case where placental pathology had been performed and a lesion had been found.

This is a noteworthy outcome. It reflects how better use of pathology services can help both clinicians and patients understand the true factors which contributed to the outcomes of unusual cases. It is also an example of how pathology can add value to clinicians, patients, and the healthcare system.

behind the registry was to have a pathologist with specialized expertise examine placentas from patients who had experienced difficult results. Unfortunately, the registry failed for lack of funding.

"The article in the newspaper made it look like we sneak around behind people's backs and steal placentas in order to keep lawyers from making a lot of money," Dr. Dyson explained. "That's not true. There's a whole other side to the story. Ob-gyns knew about the registry because those who started it made an effort to publicize it so that it would be financially viable. But, because it didn't get used enough to be financially self-sustaining, it was closed in 2003.

Payers Are Reluctant

"Frankly, it's hard to get third-party payers to pay for something like that," Dyson continued. "Most insurers use their in-plan institutions and this effort involved a pathologist who did not hold contracts with key payers. So, the problem was with payment. About the only way for the pathologists to get paid was to have the hospital pay them. When the hospital paid for it, it did so for risk management reasons—if there was a bad outcome, for instance.

"Even when the registry was running, the vast majority of the placentas that we referred for analysis were examined by the in-house pathologist," Dyson said. "When there was a big question about a particular case, then the hospitals might send it out and pay for the registry to do the exam. For instance, when the in-house pathologists couldn't answer the questions that we asked of them, or if there was a baby that had a problem, such as cerebral palsy, the placenta might be sent to the registry. When the registry did the exam, it was a far more thorough exam than was available from the in-house pathologists.

"In a typical case, results would come back to the obstetrician and would be shared with the patient, the same as with other tests," he added. "Of course, if the patient initiated

legal action before that could happen, communication with the patient would not occur and indeed they might find out about the registry only from their lawyer.

"Examining placentas is not a popular pastime for pathologists. They're difficult to handle, can be messy, and most pathologists have had minimal formal training in placental pathology."

"When it went to the registry, it was primarily because it involved defensive medicine," Dyson explained. "But that's not the primary reason we do a pathology exam of a placenta. For example, if we have someone who runs a fever during labor, we might want to know if the placenta showed signs of infection. If so, then the baby might be at risk and it would receive different treatment than if the placenta showed no signs of infection."

Medically Useful Service

Alfred Lui, M.D., President and CEO of **Pathology Inc.**, in Torrance, California, was familiar with the Cascadia Placenta Registry. "It was always my impression that they were truly trying to provide a medically useful service that would help decrease malpractice liability," he said. "By documenting true placental pathology, often the attending obstetrician could defend the delivery-related care of a patient, even if there was a bad outcome.

"Placental pathology has an increasingly important role in risk management and in learning about the various possible problems of newborns," Dr. Lui continued. "Examining placentas is not a popular pastime for pathologists. They're difficult to handle, can be messy, and most pathologists have had minimal formal training in placental pathology. In many hospitals, placental examination defaults to obstetricians. Their examination is almost always cursory at best. We believe that more thorough placental exams are a significant advance in pathology and in patient care."

Prominent Local Hospitals

The Oregonian's February 12 story said several hospitals and their parent corporations in Oregon helped finance Cascadia and sent placental materials there, including **Providence Health System**, **Legacy Health System**, **Adventist Health**, **PeaceHealth**, and **Kaiser Permanente Northwest**. Many of the women involved were unaware of the practice, the article said.

The Oregonian considered it significant that some women interviewed did not learn that a detailed pathology examination had been conducted on their placenta until they had initiated a malpractice action. In response, hospitals interviewed in the story noted that appropriate consent forms had been signed by the patient at the time they were admitted.

THE DARK REPORT observes that the lesson for pathologists and ob-gyns is to ensure that patients are told specifically through the informed consent process whenever placental material will be collected and examined and stored for use later. Doing so might require adding a sentence to the current consent forms used at the hospital and carefully explaining the implications to patients. TDR

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Patient Safety Trends

New Guidelines to Require Single-Patient Hospital Rooms

Goal is to reduce nosocomial infections, cut down medication and other errors, increase privacy

PATIENT SAFETY INITIATIVES are about to trigger another major change to the American healthcare system—a standard for single-room occupancy in hospitals.

On March 22, 2006, *The Wall Street Journal* (WSJ) reported that the **American Institute of Architects** (AIA) and the **Facility Guidelines Institute** (FGI) are preparing to issue new guidelines for hospital construction. Due out in June, the new "Guidelines for Design and Construction of Hospital and Health Care Facilities" will call for single-room occupancy for all patients.

The primary goal is to reduce the risk of nosocomial infections. However, the single room standard is expected to also reduce medication and other types of errors, cut down on the number of patient falls, and increase patient privacy.

Not A Radical Requirement

Guidelines requiring single-patient rooms are not as radical as they might first appear. The *WSJ* spoke to healthcare architects and construction companies and determined that the hospital industry is expected to spend about $30 billion in scheduled hospital construction projects in 2009. A majority of these construction projects are already planned to include 100% single-patient rooms.

This will trigger a steady evolution away from two-patient rooms toward single occupancy rooms. That's because healthcare facilities already face competitive pressure to move patients into private rooms.

To attract patients, growing numbers of hospitals have begun to offer single-occupancy rooms, more amenities, and more comfortable accommodations so that family members can stay overnight as well. What's more, affluent baby boomers prefer the additional privacy and often are willing to pay extra for private rooms.

The new hospital construction guidelines will have teeth. Hospital building authorities in 42 states, the **Joint Commission for the Accreditation of Healthcare Organizations** (JCAHO) in Chicago, and several federal agencies use the guidelines, which are updated every four years, as a standard when reviewing construction designs and plans for healthcare facilities.

Laboratory administrators and pathologists should be aware of several factors driving this new development. Obviously the cost to construct single-patient rooms is more than double-occupancy rooms. But a growing number of studies show that inpatients housed in single occupancy rooms have better outcomes—and that the overall

cost of care is reduced enough to offset the higher construction costs.

Patients recover faster in private rooms. They get fewer infections and are less likely to get the wrong medication from a hospital staff member confused about which patient in a room gets which medication.

Interestingly, having all single rooms is likely to increase occupancy rates in hospitals. That's because hospitals would no longer need to pair roommates by sex. Often, about 10% or more beds in hospitals with semiprivate rooms are unoccupied.

Patients in private rooms have fewer falls, which greatly increase hospital costs each year. When a patient stays in a private room, there are often friends and family in attendance to help when the patient has to use the bathroom, for example.

Advocates mince no words about the benefits of private rooms. Because of the additional costs from infections and other risks in semi-private rooms, Craig Zimring, Ph.D., of the **Georgia Institute of Technology College of Architecture**, stated that "we can't afford to operate U.S. hospitals that have anything other than private rooms."

His views are mirrored by Scot Latimer, President of the health architecture group at **Kurt Salmon Associates**, who stated that "unless there are extenuating circumstances, for most hospitals the semiprivate room will be a thing of the past." Despite the higher costs of building hospitals with 100% single-patient rooms, Latimer noted that "they pay for themselves very quickly and are much less expensive to operate" in the long run.

THE DARK REPORT considers the recommendation of single-patient rooms to be a significant. It is a powerful example of how patient safety initiatives will reshape the healthcare system as we know it. Efforts to accurately measure outcomes are producing detailed information about a variety of healthcare procedures and processes. This accurate and detailed information is being used to justify far-reaching changes to our healthcare system. TDR

Patients Do Better In Private Rooms

WHEN ISSUING THE RECOMMENDATION for private rooms in hospitals, the American Institute of Architects (AIA) reviewed research on patient preferences.

In its findings, the AIA said that surveys show most patients prefer single rooms because of greater privacy, reduced noise, reduced embarrassment, improved quality of sleep, opportunity for family members to stay, and avoidance of upsetting other patients. Not surprisingly, multiple occupancy rooms are associated with a lack of privacy, more noise, and sleep disturbance.

The AIA referenced research that shows hospitals are a great source of stress for patients. The reasons patients feel stressed in hospitals include a perceived lack of control, lack of privacy, noise, and crowding. Excess noise can lead to increased anxiety and pain perception, loss of sleep, and prolonged convalescence.

In contrast, the AIA's conclusion is that single rooms often afford more privacy and help reduce noise and crowding levels. Crowding contributes to higher blood pressure among patients, and research shows that private rooms often minimize a patient's sense of crowding.

In addition, patients in private rooms have more control over certain elements, such as the volume on the television and how much light comes in through the curtains. Researchers say that music can also help reduce stress among patients. In private rooms, patients can listen to music without disturbing other patients.

Lab Industry Briefs

ASCP ACQUIRES MIME'S CYTOLOGY TRAINING AND PROFICIENCY TESTING

IT WAS A BIG BREAK for pathologists and cytotechnologists involved in Pap testing. In a deal announced at the end of February, the **American Society for Clinical Pathology** (ASCP) has acquired "the complete cytology product line of the **Midwest Institute for Medical Education** (MIME)."

This eases some of the problems caused by the requirement of the **Centers for Medicare and Medicaid Services** (CMS) that, during 2006, all cytotechnologists and all pathologists examining gynecologic preparations must participate in an approved proficiency testing (PT) program.

At the time CMS announced the PT requirement, it also declared that only two PT programs were approved. One is operated by the **Maryland State Department of Health** and the other is operated by MIME. The decision to give MIME a near-exclusive lock on cytology PT training was controversial within the laboratory industry.

Since that decision became public, many laboratorians have criticized CMS for limiting approved PT programs to just two sources: a state health agency and MIME. There have also been criticisms about the fundamental need for a federally-administrated proficiency testing program in cytology, as well the design of the program as mandated.

However, there is another dimension to this story which was underplayed. Informed sources asked how and why MIME came to be selected by CMS over other more-qualified providers of laboratory PT training. CMS has never answered those questions, nor has it taken steps to dispel accusations that favoritism or inside connections played a key role in the selection of MIME as the near-exclusive source of all cytology PT training done in the United States.

In fact, the questions about MIME are legitimate. Ongoing investigations by THE DARK REPORT in recent months have uncovered several facts that call into question the original decision by CMS to make MIME the primary source of cytology PT programs.

That's because MIME was a new enterprise. It was established in recent years by **Diagnostic Cytology Laboratories, Inc**. (DCL) of Indianapolis, Indiana. This is a cytology testing laboratory that has had its share of financial problems during the past five years.

Between 2002 and 2004, numerous federal tax liens and state tax warrants were filed against DCL and cleared as payment was received. During these same years, MIME was operated as a subsidiary of DCL. It was eventually split off into a separate company before CMS selected MIME to be the primary source for cytology proficiency testing.

Given this background, and given the fact that MIME had never operated a PT program of large size and scope, it certainly raises important questions about the process CMS used to select a cytology PT vendor and whether personal influence played a role in the selection of MIME.

Further, the fact that ASCP has acquired MIME's complete cytology product line at this time is likely to be directly linked to MIME's lack of cap-

ital and expertise to operate a large scale, national cytology PT program.

Thus, it is a positive development that ASCP will assume MIME's role in federal cytology proficiency testing. However, MIME's exit from the scene will not quiet those critics of cytology PT as it is currently constituted. These criticisms are directed toward the relevance of current cytology PT requirements and whether they appropriately reflect current technologies and clinical standards of care involving cytology.

HOSPITAL LAB LOSES MEDICARE LICENSE IN VICTORVILLE, CALIF.

FALLOUT CONTINUES FROM THE SERIOUS PROBLEMS discovered at the laboratory of **Maryland General Hospital** in Baltimore, Maryland in the winter of 2004. Government regulators are taking more decisive action when laboratory deficiencies are uncovered.

In recent months, several labs have been the targets of regulatory action. In Victorville, California, the **Centers for Medicare and Medicaid Services** (CMS) has suspended payments to the laboratory at **Victor Valley Community Hospital**.

CMS took enforcement action after determining that the hospital laboratory had failed surveys, particularly in bacteriology. At one point, for a five-day period, the lab was deemed in "immediate jeopardy," an indication that the agency considered the health of patients was at risk.

Medicare payments to the laboratory were terminated on October 5, 2005. Since that date, fines of $3,000 per day have accrued and now total over $426,000. Hospital administration has filed a written appeal with a California administrative law judge. Hospital officials also emphatically state that patient care has not been put in jeopardy.

No resolution has been made public. Discussions are ongoing between CMS and administrators at Victor Valley Medical Center.

In Maryland, the State Department of Health has increased its scrutiny of laboratories following the widely-publicized failures of the laboratory at Maryland General Hospital. Last fall, health officials in Maryland cited a laboratory facility of **Quest Diagnostics Incorporated** in Southwest Baltimore for a number of deficiencies. During inspections of the Quest Diagnostics laboratory by state health officials on October 22, 2004, April 18, 2005, and September 19, 2005, it was determined that the laboratory was reporting inaccurate test results for several assays. These included tests for thyroid-stimulating hormone and testosterone, among others.

In a week-long follow-up inspection in February, state officials also determined that the automated chemistry department at the Quest laboratory was understaffed and lacked the number of employees needed to allow time for proper documentation of quality control and other essential steps. The lab was cited for this situation. None of the incidents identified by healthcare inspectors was considered to have been life-threatening to patients affected by the problems.

THE DARK REPORT sees these two enforcement actions against laboratories as signals that regulatory scrutiny of laboratory operations will be increasing. Given the bad publicity following the MGH laboratory debacle, government laboratory regulators are on notice that the media will pounce on any juicy story that lab inspectors were "asleep at the switch." To forestall such situations, lab regulators will be quicker to formally cite laboratories where deficiencies are discovered. TDR

INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

Another private lab company appears to have sold for a strong price. On March 21, 2006, **American Capital Strategies Ltd.** of Bethesda, Maryland, announced that it had invested $79.5 million in **Redwood Toxicology Laboratory Inc.**, a drugs-of-abuse testing laboratory based in Santa Rosa, California. The financing package includes a revolving credit facility, senior subordinated debt, along with enough preferred and common stock to give American Capital Strategies a 67% equity interest in Redwood Toxicology Laboratory.

MORE ON: Redwood Tox

Redwood Toxicology Laboratory has annual revenues of approximately $30 million. So the announced investment of $79.5 million in debt and equity by American Capital Strategies indicates an aggressive valuation for a lab company serving the highly-competitive drugs-of-abuse testing marketplace. Company founder Bob Mount and his executive team hold the balance of the lab firm's equity.

INTEL PREPARES SPECIAL PRODUCTS FOR HEALTHCARE

Last year, **Intel Corporation** disclosed its plans to focus on healthcare and develop specialized products designed to meet the needs of hospitals, physicians, patients, and the patient's family members. Intel will use two strategies to develop its healthcare business. First, it wants to take an active role in developing new IT (information technology) standards for hospitals and clinics. In these settings, it is often difficult for different kinds of medical equipment to easily exchange information. Second, Intel is developing specific products tailored expressly to meet the needs of healthcare providers and patients in their homes.

ADD TO: Intel in Healthcare

For the past year, a special team from Intel Corporation has been collecting information about problems in how physicians and consumers use healthcare information. In recent weeks, Intel has publicly showed a prototype of a wireless-enabled, tablet-style computer designed for use by physicians and nurses. Among other things, when the clinician approaches a patient wearing an RFID (radio frequency identification) tag, the computer would automatically retrieve and present that patient's medical file. This computer also has a built-in camera to allow the clinicians to share data with medical professionals in other locations. with this initiative, Intel is joining **IBM**, **Motorola**, and several other major IT vendors that have declared their intention to develop a major presence in the healthcare sector.

TRANSITIONS

• **Pathology Partners, Inc.**, of Dallas, Texas, has a new CEO. Gail Marcus is filling the position left vacant when Stephen Spotts departed from the company in early February. Marcus comes from outside the laboratory industry. She has previous work experience with Pathology Partners' Chairman, David Halbert. Halbert owns **Caris, Ltd.**, the investment fund which holds a majority interest in Pathology Partners.

That's all the insider intelligence for this report. Look for the next briefing on Monday, May 1, 2006.

PREVIEW #5

EXECUTIVE WAR COLLEGE

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Using Middleware at Mid America Clinical Labs to Boost Productivity and Slash Costs

Middleware is fast-becoming both a rapid and cost-effective solution for many laboratories. Middleware—defined in basic terms as any type of software product that sits between the LIS, instruments, and other software systems and performs defined functions—is a key component of the informatics strategy at Mid America Clinical Laboratories in Indianapolis. Discover how frequently Mid America has used a middleware solution to improve operational efficiency, feed real-time data to clients and internal customers, and automate work processes to eliminate manual steps and free up lab labor for higher

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UPCOMING...

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- ***How One Lab Is Bypassing its LIS Vendor for Middleware Solutions That Trigger Major Operational Gains.***

- ***THE DARK REPORT In Korea: News from Lab Automation Symposium and Lab Site Visits.***

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