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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...

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Founder & Publisher

Deep-Discount Lab Prices to Haunt All California Labs

FOR MORE THAN 20 YEARS, THE CLINICAL LAB INDUSTRY been marked by a fundamental schism. On one side of the schism are the public lab companies that have aggressively used deeply-discounted loss-leader pricing practices when negotiating managed care contracts to capture market share.

On the other side of the schism are the majority of lab organizations, ranging from independent labs and hospital lab outreach programs to private pathology group practices. These are the labs that understood the long-term financial harm to the laboratory medicine profession as payers wanted to extract the same deeply-discounted lab test prices from all the clinical labs in their service regions.

Now all labs in California are about to reap the consequences from the public lab companies' liberal use of such deeply-discounted lab test prices in their managed care contracting practices. As a consequence of the whistleblower lawsuit initiated in California in 2005 and settled in 2011, the California state legislature has enacted laws that will result in a 25% to 30% cut in Medi-Cal clinical lab test fees, according to the executive director of the **California Clinical Laboratory Association**. These reduced fees will take effect on July 1, 2015. *(See pages 6-8.)*

This situation came about because of the price information disclosed in the whistleblower lawsuit. Once state healthcare officials saw the rock-bottom prices the two blood brothers were giving to managed care plans, IPAs, and other preferred customers in California, they took steps to ensure that the Medi-Cal program got those same deeply-discounted prices.

But that is just the story in one state. Congress and Medicare officials are embarked on a comparable effort to lower Medicare Part B clinical lab test fees to the similar levels that the two blood brothers give to their preferred customers, including **UnitedHealthcare**, **Aetna**, and the state Blues, for example.

Recall that it was in 2011 when Senators Baucus and Grassley issued subpoenas to the two national labs and three health insurers for documents associated with their lab services contracts. Not coincidentally, this followed the public disclosure of the settlements in the California whistleblower case.

Thus, the lab test market pricing requirement in the PAMA legislation can be considered an action by the federal government to ensure that the Medicare program gets the same deeply-discounted lab test prices that the national lab companies provide to health insurance companies. TDR

Opko Pays $1.47 Billion To Buy Bio-Reference Lab

Nation's third largest lab company to become business unit of a pharma and diagnostics firm

CEO SUMMARY: It's a case of the little fish gobbling the big fish, as Opko Health—with revenue of $91 million—will be acquiring Bio-Reference Laboratories, with revenue of $832 million. But the more interesting aspect of the story is that the CEO of Opko Health is a physician worth $5 billion and highly-respected by Wall Street. It could be that Bio-Reference CEO Marc Grodman, M.D., has gained a shrewd advisor and powerful ally in Phillip Frost, M.D., the Chair and CEO of Opko Health.

MANY LAB INDUSTRY EXPERTS and Wall Street investors were caught by surprise when, on June 2, they learned that **Opko Health Inc.**, of Miami, Florida, had agreed to pay $1.47 billion in an all-stock deal to acquire **Bio-Reference Laboratories Inc.**, of Elmwood Park, New Jersey.

Bio-Reference is the nation's third largest publicly-traded lab company and had revenue of $832 million for its fiscal year ending October 31, 2014. Opko Health, by contrast, is a much smaller company. It posted revenue of $91 million for 2014. Opko is focused on pharmaceuticals and diagnostics. Currently it has only a small presence in the clinical laboratory testing marketplace.

There were several reasons why the lab industry and Wall Street were caught off guard by this acquisition announcement. First, there was no prior indication or rumor that Bio-Reference had an interest in being acquired. Second, the acquiring company is much smaller, with just one-eighth the annual revenue of BRLI.

Third, Opko is better known for its pharmaceutical products than its diagnostic services. Fourth, many financial analysts have always assumed that, were Bio-Reference Laboratories to be sold, the most likely purchasers would be **Laboratory Corporation of America** or **Quest Diagnostics Incorporated**—or even a big private equity company—but not a relatively small company involved in therapeutic drugs and diagnostics.

Opko and BRLI expect this transaction to close in the second half of 2015, subject to regulatory approvals. Officials

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stated that Bio-Reference Laboratories would continue to operate with its existing management team and would begin distributing Opko's diagnostic products and lab testing services following the completion of the sale.

Wall Street's Mixed Response

News of BRLI's acquisition met with a mixed response by investors and analysts on Wall Street. For example, Todd Campbell at *Investopedia* saw benefits to Opko Health from this deal. He wrote, "As a result, Opko Health's acquisition instantly transforms it from a small-cap company with little revenue and no profit into a lab testing leader with annualized revenue north of $900 million that can help offset some of Opko Health's spending."

Other investors voted with their feet against the deal. In the days following the acquisition announcement, Opko shares fell from $19 on Wednesday, June 3 to under $16 by Friday, June 12. Because Opko is swapping its shares for BRLI, this reduces the market value of the transaction.

Assuming that the acquisition is completed during the second half of 2015, the question then becomes: what is next for Bio-Reference Labs? For the better part of two decades, it has been one of the nation's fastest-growing public lab companies. During this time, it regularly posted quarterly gains greater than 10% to 15% in revenue and specimen volume.

Both a Local, National Lab

Bio-Reference has also accomplished a unique feat. Within its core geography of New York City and the Tri-State Metro, it provides the full range of routine, reference, and esoteric testing services to office-based physicians in competition with Laboratory Corporation of America and Quest Diagnostics Incorporated.

More significantly, from this foundation, Bio-Reference has built a steadily-growing regional and national business in reference and esoteric testing. During its quarterly conference call on Monday, June 8, company executives reported that reference and esoteric testing represented 68% of total revenue for the quarter ending April 30, 2015.

Because of this quite large proportion of reference and esoteric testing, in its overall lab test mix, Bio-Reference Laboratories enjoys a very high average revenue per requisition. BRLI reported that revenue per patient was $86.69 in the most recent quarter. This was a 3% increase from the $84.18 recorded for second quarter of 2014. It is almost double the average revenue-per-requisition generally reported by BRLI's two large national lab competitors, which is in the $45 range.

Overlooked Aspect Of Deal

One aspect of this acquisition that most financial analysts have overlooked is the fact that Opko Health has a Chairman and CEO who is widely-respected by the financial community. He is Phillip Frost, M.D. *Forbes* estimates his net worth at $5 billion.

Frost has been active in the pharmaceuticals industry since the mid-1980s. He is probably best known for having led **Ivax Pharmaceuticals**, a generic drugmaker, from small size in 1987 to a $7.6 billion sale to **Teva Pharmaceuticals** in 2005.

Frost was a dermatologist and served as Chairman of the Department of Dermatology at **Mt. Sinai Medical Center of Greater Miami**, in Miami Beach, Florida from 1972 to 1990.

As *Forbes* noted, "While practicing in Miami in the 1960s, he (Frost) tinkered with a disposable device to make biopsies easier. He recognized the tool had potential both in the examination room and the marketplace, and partnered with Michael Jaharis to build a company around it. Jaharis took care of the boardroom and ran the day to day. Frost stayed in the lab and added new patents. Their duet was a

hit and Jaharis has become a billionaire too. They sold **Key Pharmaceuticals** to **Schering-Plough** in 1986 for $835 million."

Experience With Diagnostics

As this profile shows, Frost has direct clinical experience with biopsies and diagnostic technology. He understands the potential for clinical lab testing to significantly improve diagnostic accuracy and patient outcomes.

Thus, Frost and his executive team may fully appreciate the way Bio-Reference Laboratories built a thriving business on sophisticated molecular diagnostics and genetic testing. They could see some useful synergies among the products under development by both companies.

This opportunity was specifically mentioned in the press release announcing the acquisition. The two companies said, "Through GeneDx, Bio-Reference Laboratories' genetic sequencing laboratory, and GenPath Diagnostics, its Oncology and Women's Health business units, Bio-Reference Laboratories has accumulated a vast array of genetic and genomics data that OPKO will make available to industry and academic scientists to enhance their drug discovery and clinical trial programs."

New Diagnostic Opportunity

Another element to this pending acquisition pathologists and clinical laboratory managers should recognize is that ongoing advances in molecular and genetic technology are creating new opportunities to apply these developments to clinical care in unique ways. Companion diagnostics—a specific clinical lab test to determine how the patient may benefit from a specific therapeutic drug—is just one example of such an opportunity. Therefore, we may see other unexpected buyers come into the market and acquire clinical laboratory companies for these reasons. TDR

In 2012, Okpo Acquired Oppenheimer Urologic Lab

ON NOVEMBER 19, 2012, Opko Healthcare announced an agreement to acquire **Prost-Data, Inc.**, the owner of **OURLab** (also known as Oppenheimer Urologic Reference Laboratory).

At that time, in an exclusive interview with THE DARK REPORT, Jonathan Oppenheimer, M.D., the founder of OURLab, discussed the reasons behind his interest in selling his lab company to Opko. Among those reasons was the opportunity to go beyond lab testing and collaborate on therapeutic solutions. *(See TDR, November 19, 2012.)*

"This merger is important for OURLab because it creates the opportunity to use our existing resource base in three ways," explained Oppenheimer. "First, because of proprietary diagnostic and therapeutic technologies at Opko Health, our clinicians will be engaged in activities that go beyond laboratory medicine and pathology.

"Second, it leverages our sales force by giving them more products to sell," noted Oppenheimer. "Third, in addition to our work in diagnostic medicine, we can now get involved in the development of pharmaceuticals, which is a fast-growing area of medicine today." *(See TDR, November 19, 2102.)*

One specific opportunity for synergy in Opko's acquisition of OURLab was Opko's 4Kscore test. This proprietary assay uses a blood specimen to provide the patient and the physician with a risk score for prostate cancer. Both companies expected that OURLab would be a channel to market the 4Kscore test and other diagnostic products developed by Opko.

The press release announcing the agreement between Opko and Bio-Reference Laboratories, noted that BRLI would distribute Opko's diagnostic products. That would include the Opko's 4Kscore assay.

Medi-Cal to Cut Lab Pay On July 1 by 25% to 30%

➤Latest round of deep lab price cuts follows several years of other lab test fee reductions

➤➤CEO SUMMARY: Since 2011, state officials in California have aggressively cut laboratory testing fees for Medi-Cal, the state's Medicaid program. Now state officials say they will implement a new methodology next month for determining lab testing fees. The new methodology is based on lab pricing data produced as a result of whistleblower lawsuits against labs that were settled in 2011. Should prices fall below the costs of performing these tests, the Medi-Cal program may see legal challenges from the lab industry.

CLINICAL LABS IN CALIFORNIA will face a cut in payment rates of 25% to 30% next week for laboratory tests for any Medi-Cal patient, stated Michael Arnold, Executive Director of the **California Clinical Laboratory Association**.

"These reduced payment rates in California result from whistleblower suits filed in 2005," noted Arnold. "One result of the lawsuits was that state officials noticed that clinical labs were taking payment rates from commercial insurers that were lower than what Medi-Cal was paying. Under state law, Medi-Cal should pay the lowest rates."

In 2011, state officials settled those whistleblower cases when the defendant labs paid millions of dollars to resolve the charges without admitting guilt. "In response to the information surfaced during the investigation, state officials have acted to reduce what Medi-Cal pays to the state's 1,400 clinical laboratories," Arnold said. "Of those 1,400 labs, we know that about 400 to 500 are freestanding independent labs, and the rest are labs based in physician offices and in hospitals."

Arnold explained this change and others affecting clinical laboratories in California as a speaker on a panel at THE DARK REPORT'S 20th anniversary *Executive War College* last month.

In the whistleblower cases, state officials charged **Quest Diagnostics Incorporated**, **Laboratory Corporation of America**, and five other lab companies with failing to comply with California's regulations so that the Medi-Cal program overpaid the defendant labs for medical lab testing services.

➤Settlements In Qui Tam Suits

The suit resulted in settlements between the clinical labs and state Attorney General Kamala D. Harris. In May 2011, Quest Diagnostics agreed to pay $241 million to settle the charges. In August 2011, Harris announced a $49.5 million settlement with LabCorp to settle charges that Medi-Cal overpaid for lab testing services under a similar scheme. *(See TDRs June 13 and September 26, 2011.)*

In these whistleblower cases, the lab companies were accused of providing mil-

lions of dollars in low-cost or below-cost testing to health insurers. In return, the insurers would require their network physicians—who also served Medi-Cal patients—to send lab tests to the defendant labs in the lawsuit. The labs then billed Medi-Cal much greater amounts for identical tests in a scheme called pull-through billing. LabCorp offered some tests to private insurers for as low as $1, *CBS News* reported.

The payment rates violated rules for the state's Medi-Cal program because private insurance companies were getting the lowest lab test rates when state law requires that all providers offer Medi-Cal the lowest rate for healthcare services.

After the settlements, California officials wanted to change the state's payment regulations to ensure compliance with California Medi-Cal statutes. "State officials noticed that Medi-Cal was not getting the lowest rates," explained Arnold. "And those officials wanted to rectify that situation."

Legislature Gets Involved

Acting on recommendations from the state Department of Finance and the Department of Health Care Services, the legislature agreed to cut the rates Medi-Cal pays to clinical labs.

"Here's how it happened," noted Arnold. "In 2011, the legislature faced budget problems and passed Assembly Bill 97, making a price cut retroactive to June 1, 2011. "That meant that Medi-Cal payment amounts for lab services on or after that date were reduced by 10%. It was as if the state assembly was saying, 'We will reduce your payments by 10%.' Much of the reason for this reduction was the *qui tam* lawsuits that were settled in 2011.

"Then, in 2012, the state faced more budget problems and the legislature passed AB 1494, which imposed an additional 10% payment reduction on top of the payment reduction that labs got under AB 97," he continued. "And, again, the legislature made those changes retroactive, this time to

New York DOH Changing Proficiency Test Process

IN NEW YORK, the state Department of Health does not recognize any proficiency testing program other than its own. That situation is about to change, however.

"In the past, New York felt it did proficiency testing better than anyone else and that is why it made all labs abide by its own proficiency testing (PT) standards," observed Thomas Rafalsky, President and General Counsel of the **New York State Clinical Laboratory Association**. "But now that process will change."

Starting next year, the New York State Department of Health will allow other PT providers recognized by the federal **Centers for Medicare & Medicaid Services** to run PT programs that will be recognized by New York State. NYSDOH will compete against other PT providers.

"Many labs use PT services from a variety of PT providers," said Rafalsky. "In such situations, they must still use the New York State proficiency testing service. This results in unnecessary duplication and additional expenses. For large labs, this duplication easily could cost hundreds of thousands of dollars for multiple PT programs.

"Many labs feel the staff time needed for the different PT programs is more onerous than the additional cost," he added. "In response to complaints from our members, over the past two years, we've negotiated this matter with the state DOH. State officials finally relented, agreeing to recognize the PT results of other CMS-approved entities.

"All labs operating in New York State will get a letter from NYSDOH in September or October outlining this new process," he said. "By approximately December 1, labs will need to choose a PT entity for calendar year 2016. NYSDOH will continue to run a PT program, but on a smaller scale. The redundancies will be eliminated, which is a major accomplishment."

July 1, 2012. In addition, AB 1494 included a second provision that required state officials to develop a new methodology for reimbursement rates that Medi-Cal would pay to clinical laboratories.

"As part of the new rate methodology, the assembly told the state Department of Health Care Services to collect data on the lowest rates that labs would accept from commercial payers," stated Arnold. "This request required labs to do a significant amount of work to collect all the payment data. CCLA complained that state officials were asking for too much information and had a series of meetings with state officials. Ultimately, Medi-Cal officials agreed to reduce the number of CPT codes for which labs would have to report all prices they accepted from different payers.

"But then, not all labs reported what commercial insurers paid them," he added. "In fact, only about 60 or 70 labs out of about 1,400 reported their data to state officials. That's a big problem because it is believed that many labs that are likely to be getting more for reimbursement probably didn't report because they were smaller laboratories and found the reporting to be very difficult. But the expense of collecting this pricing data was prohibitive for these smaller labs.

Few Labs Reported Prices

"The fact that so few labs reported the price data is important for another reason," continued Arnold. "Under the Protect Access to Medicare Act (PAMA) which the U.S. Congress passed last year, the federal **Centers for Medicare & Medicaid Services** will be collecting price data from clinical labs. If all labs don't report their price data, it is likely to skew the results. And if the results are developed from incomplete data, CMS could set new rates based on flawed data. But that's a different topic.

"After the 60 to 70 California labs submitted their price data, the state analyzed this information and decided to toss out all the prices that were above 80% of Medicare because state law says Medi-Cal can't pay more than 80% of Medicare," observed Arnold. "Of course, CCLA complained that tossing out those numbers pushed the average for each CPT code much lower, but state officials ignored that objection.

Weighted Average Of Prices

"Medi-Cal officials said they would determine the weighted average of test prices and then apply the 10% cuts enacted under AB 97," he said. "But the price cuts under AB 1494 were eliminated because rates were being adjusted under the new reimbursement methodology.

"The end result of these changes is that clinical labs will get a 25% to 30% cut when all these cuts go into effect on July 1," commented Arnold. "Now, having said all that, we still don't know exactly if this new methodology will be implemented or how it will be implemented.

"We believe it will be put in place because that's what state officials said," he said. "We have tried to reach state officials to ask them for specific details, but so far we have had no response. We just know they said the new methodology would go into effect on July 1.

"Therefore, labs will have to adjust to new Medi-Cal rates starting next month, but there are additional problems clinical labs face in California," added Arnold. "Labs involved in personalized medicine in California—and we have many of them—are extremely upset about CMS practices with respect to local coverage determinations (LCDs) that affect what Medicare and Medi-Cal will pay for certain genetic and molecular tests."

CCLA filed a lawsuit against HHS last year over this matter, but that lawsuit was recently dismissed. TDR

—Joseph Burns

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IVD Market Update

LabCorp, Sysmex Will Collaborate To Develop Liquid Biopsy Tests

NeoGenomics announces 12 assays with liquid biopsy technology to detect tumors, monitor patients' response

ANOTHER SIGN OF HEALTHCARE'S TRANSFORMATION came on June 1 when **Sysmex Corporation** of Kobe, Japan, and **Laboratory Corporation of America** in Burlington, North Carolina, announced a unique collaboration to develop blood-based molecular diagnostic tests for cancer.

The collaboration calls for Sysmex, a major *in vitro* diagnostics (IVD) manufacturer with expertise in hematology testing, to work with LabCorp. Efforts will center around two assays developed at Sysmex Inostics, called OncoBEAM and Plasma-Sequencing.

These assays allow clinicians to do a molecular genetic analysis of cell-free tumor DNA from blood samples. Often called a liquid biopsy, this technology is a non-invasive method of determining the mutational status of a cancer patient's tumor and for selecting appropriate therapeutic agents. Sysmex and LabCorp said this technology can eliminate the need for further biopsies.

An interesting twist in this story is that LabCorp can give Sysmex access to patients in clinical trials for medications that oncologists would use for cancer. That access comes through LabCorp's recent acquisition of **Covance**, which it completed in February. Sysmex Inostics will provide reagents and services to allow Covance to provide OncoBEAM and plasma-sequencing testing services to support clinical trials in oncology. Also, Sysmex and LabCorp will seek ways to develop commercial applications to use Sysmex technologies in clinical diagnostics.

Another lab company working on developing liquid biopsy technology is **NeoGenomics Inc.**, of Fort Myers, Florida. Earlier this month, NeoGenomics announced the launch of 12 liquid biopsy tests that use next-generation sequencing and other advanced molecular technologies. Called NeoLAB tests, these assays use cell-free circulating DNA and RNA in blood plasma to identify molecular abnormalities in the bone marrow without the need for a bone marrow biopsy.

Use of Blood Specimens

NeoGenomics said more than 600,000 bone marrow biopsies are done each year to diagnose and monitor treatment of patients with hematologic cancers. The new tests may eliminate the need for such biopsies. Cell-free testing is based on the concept that hematologic cells release DNA, RNA, and protein into circulation when the cells are immersed in blood. Cell-free circulating DNA, RNA and protein are called exosomes, microvesicles, apoptotic bodies, or simply DNA- or RNA-protein complexes, NeoGenomics said.

The ability to use liquid biopsies successfully has been a goal of diagnostics companies because it is less invasive than traditional biopsies. Therefore, these assays could allow for earlier detection of cancer in the bloodstream before clinicians can detect a tumor. TDR

New Precision Medicine Initiative Now Put on Hold?

Medicare Ends Coverage for Genetic Drug-Sensitivity Tests

CEO SUMMARY: Medicare's decision to cease covering many pharmacogenomic tests puts as many as 19 million Americans who have genetic variations affecting their response to medications at risk. These medications are commonly prescribed for patients with cardiovascular disease, pain, depression, anxiety, and cancer. Meanwhile, medical centers such as Mayo Clinic are conducting clinical studies to collect evidence that appropriate use of pharmacogenomic tests can improve patient outcomes while also reducing the cost of care.

WHAT THE FEDERAL GOVERNMENT giveth with one hand, it will often taketh away with the other hand. It might be argued that this is true of federal support of pharmacogenomic testing—particularly for those tests clinical laboratories use to identify how patients metabolize many types of prescription drugs.

The federal government hand that giveth is the $215 million initiative announced by President Obama in January to foster the development of precision medicine. Government officials said that the **National Institutes of Health** and other departments would use the funds to generate the scientific evidence to move the concept of personalized medicine into clinical practice.

The federal government hand that taketh away on this matter is the Medicare program. Since last fall, the nation's Medicare Administrative Contractors (MACs) have been discontinuing payment for pharmacogenomic testing that identifies how patients metabolize and respond to prescription drugs. As of June 22, all MACs had stopped paying for these tests. The last one, **Noridian**, ended payment for these tests on June 22.

"As many as 19 million Americans could be affected by this decision," stated Kristine Ashcraft, Chief Operating Officer of **Genelex**, a pharmacogenomic testing company in Seattle, Washington. "That's because about 75% of Americans have genetic variations affecting their response to medications. These medications are commonly prescribed drugs for patients with cardiovascular disease, pain, depression, anxiety, and cancer. When you consider that 4% of Medicare spending is for hospitalizations caused by adverse drug reactions, taking away coverage for tools that can help combat this problem is short-sighted."

In its Local Coverage Determination (LCD) effective June 22, Noridian said it would end genetic testing to assess patients taking some medications and that for other medications, it would await definitive utility for such testing. In the LCD, Noridian said it ended payment for all genetic testing associated with all medications related to *CYP2C9* (CPT 81227) and VKORC1 (CPT 81355). For genetic testing for medications related to *CYP2C19* (CPT 81225) and *CYP2D6* (CPT 81226), Noridian ended payment until definitive clinical utility is established. Testing for response to medications related to *CYP2C19* and *CYP2D6* would be limited for patients with certain indications, Noridian said.

"This decision is designed to save money at the expense of patient care," said John Logan Black, III, M.D., Co-Director, Personalized Genomics Laboratory and Vice Chair for Business Development in the Department of Laboratory Medicine and Pathology at **Mayo Clinic** in Rochester, Minnesota. "It comes down to dollars and cents and not really what patients need," he explained. "Medicare officials are trying to control costs by saying they haven't seen enough benefit from these tests.

Pharmacogenomic Testing

"However, it has long been considered that pharmacogenomic testing is the low-hanging fruit from the Human Genome Project, because these tests give us a lot of personalized information about patients," he commented. "But now critics say it's too hard to implement or insurers say they're worried about the costs to implement this testing."

Black pointed out that, even as Medicare ends or limits such coverage, the federal **Food and Drug Administration** recommends pharmacogenomic tests for medications. "Not only is such genetic testing recommended, but, in many cases, FDA clearance requires pharmaceutical companies to print those recommendations for genetic testing on the product information forms patients receive when prescribed these medications," he explained.

"The FDA's website shows the Table of Pharmacogenomic Biomarkers in Drug Labeling," he continued. "This is a list of

medications that pharmacogenomic biomarkers affect. These are biomarkers—meaning pharmacogenomic targets—that the FDA requires in drug labeling.

"On the list are a number of cytochrome P450s that require disclosure on drug labels as either cautionary, or, in some cases, the drug label contains information that says, basically, 'If you're going to use a specific dose, you (meaning the treating physician) should test this cytochrome P450.' In some cases it says you should just test cytochrome P450 regardless of dosing," he said.

Providers Caught in Middle

"So now what happens when Medicare payment doesn't follow those recommendations?" Black asked. "It puts healthcare providers in a difficult position because—on one hand the FDA says, 'You should test this patient'—and on the other hand, Medicare says, 'We're not going to pay for it.' The patient gets caught squarely in the middle and may end up paying for that genetic test out-of-pocket. Or, if the patient decides not to be tested, then that patient may be at increased risk.

"The FDA is an important and reliable source of information on these biomarkers and how they interact with some of the most common medications," continued Black. "But in addition to what the FDA says, the recommendations of the **Clinical Pharmacogenetics Implementation Consortium** should also be considered. CPIC publishes articles used to set practice guidance risk. This information is based on published literature.

PLAVIX (clopidogrel bisulfate) tablets
Initial U.S. Approval: 1997

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)**
- **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)**

The FDA warning for Plavix (clopidogrel bisulfate) alerts physicians about possible diminished effectiveness of this medication in patients who are poor metabolizers and the need for pharmacogenomic tests for *CYP2C19* to identify those patients.

"After looking over the literature, this committee evaluates the research on these various medications and biomarker studies and publishes practice guidance on the use of pharmacogenomic tests," he stated. "For issues in which clinicians need practice guidance, CPIC will put together a group of experts who write and publish a paper on the issue. For many of us, that paper then becomes the practice guidance for the use of pharmacogenomic tests in clinical practice.

"So once again, clinicians have a conundrum because these guidance documents are published, highly-regarded expert opinions," emphasized Black. "Many of us in the field consider them to be the guidance documents for pharmacogenomics.

"So now this best-practice guidance is published and available to all," said Black. "Therefore, I can envision a physician potentially being involved in litigation where the patient alleges that the physician didn't follow what is considered 'practice guidance' in this area and the patient ended up with a horrible side effect. I'm not aware of any case like that, but it's possible."

Up to this point, Black was discussing the most common type of pharmacogenomic testing, which is reactive testing. "A common example of reactive testing is when a patient with heart disease gets a stent and the cardiologist prescribes clopidogrel, which is an anti-platelet agent, and the gene involved is *CYP2C19*," he said.

"The FDA has issued a boxed warning for the brand name of this drug, Plavix, and it has issued precautions on this med-

Mayo Physician Says: 'This Is Not Some Cool Idea. Pharmacogenomic Tests Improve Patient Care'

HERE'S A STORY ABOUT A REAL PATIENT WHO would have benefited from proactive pharmacogenetic testing, said John Logan Black, III, M.D., Co-Director of the Personalized Genomics Laboratory at Mayo Clinic. "Unfortunately, this case is not unusual," he stated.

"I heard from a clinician that a patient came in from a nursing home after having a pulmonary embolism," recalled Black. "The doctor prescribed warfarin and sent the patient back to the nursing home. When the patient returned a week later, his INR was off the chart, and it wouldn't come down. And the patient was coughing up blood.

"To reverse the effects of warfarin, the physician prescribed vitamin K, and the INR came down a bit, but wouldn't stay down," he said. "Now the clinician was concerned that the patient got rat poisoning in the nursing home, so he considered filing a report of a case of a patient getting rat poison. But before he did, he ordered the *CYP2C9/VKORC1* test for warfarin sensitivity.

"The result showed that the patient had the worst genotype possible for taking warfarin. Thus, he's going to be at high risk for bleeding," noted Black. "This patient will have a very high INR on the usual doses of warfarin. It may be acceptable to give him maybe one-fifth of a normal dose. But the physician would need to be extremely careful with any dosage of warfarin. It might be better to prescribe a different drug.

"The point of this story is that pharmacogenomic testing produces real results that make a significant difference for people," concluded Black. "This is not some kind of genetic testing that we think might be a good idea to try. It's not something someone thought would be cool to do because we have the ability to assess genetic information. Every day, I see how these pharmacogenomic tests improve patient care."

ication regarding dosage and administration," stated Black. "A boxed warning is FDA's most serious warning. It says the drug has diminished effectiveness in those individuals who are *CYP2C19* poor metabolizers." *(See boxed warning in the sidebar on page 12.)*

"Normally, a patient would get this genetic test after starting therapy and the indication became apparent to the physician," Black explained. "So reactive testing is one way to proceed.

"Now, what some medical centers, including Mayo Clinic, are moving toward is proactive testing," noted Black. "When a patient falls into a demographic group that has increased risk factors indicating the possibility of developing heart disease, as an example, the physician may want to do the *CYP2C19* or other testing long before the patient actually needs medication.

"Then, in the future, if and when that patient needs a stent, the physician knows the most appropriate drug to use," he said, "That is because an alert fires in the medical record automatically, telling the clinician immediately which medication to prescribe.

"This prevents a patient from getting a medication that otherwise may be as effective as water," emphasized Black. "This method of testing puts these patients on the correct treatment regimen the first time to protect them from premature stent closure and possible cardiac death. That's one example of the clinical value of these tests.

Higher Risk Of Bleeding

"A physician could do proactive testing on patients who need warfarin," he continued. "Should I see a genotype indicating high risk, then I have to call the treating clinician to warn that this patient is at a high risk of

FDA Recognizes Need For Pharmacogenomics

On its website, the Food and Drug Administration publishes a table of pharmacogenomic biomarkers used in drug labeling. The table lists FDA-approved drugs with pharmacogenomic information in their labels.

On the list are 171 prescription medications. The labeling for some, but not all, of the medications includes specific actions that clinicians should take based on the biomarker information.

"Pharmacogenomics can play an important role in identifying responders and nonresponders to medications, avoiding adverse events, and optimizing drug dose," the FDA site says. When the FDA requires a warning on a drug's product label, the warning may contain information on drug exposure and clinical response variability, the risks for adverse events, genotype-specific dosing, mechanisms of drug action, and polymorphic drug target and disposition genes.

The biomarkers the FDA lists include germline or somatic gene variants, functional deficiencies, expression changes, and chromosomal abnormalities. The FDA website also lists some protein biomarkers used to select patients for treatment.

"The FDA's biomarker list demonstrates how many indications for pharmacogenomic testing are currently identified and considered clinically relevant," noted John Logan Black, III, M.D., Co-Director, Personalized Genomics Laboratory at Mayo Clinic. "Some of those on the list may be a bit soft and that reflects caution on the part of the FDA.

"But for other biomarkers, there is a strong indication that genetic testing is needed," commented Black. "For example, clinicians need to consider checking *CYP2C19* if a patient is prescribed the antidepressant citalopram at doses greater than 20mg due to increased risk of a cardiac condition known as long QT syndrome. The physician would not know that fact if this genetic test were not performed."

having a very high INR—and a higher risk of bleeding—if that patient gets the usual doses of warfarin.

"For these cases, we typically don't do proactive testing and so patients are put on warfarin," he said. "Then, when these patients have problems, the physician must determine what happened. With Medicare no longer reimbursing for these pharmacogenomic tests, the question becomes, 'Who will pay for this genetic testing for a patient in a nursing home?'

"Some patients who are nursing-home bound will be able to pay and some won't," observed Black. "Basically, these Medicare patients will be denied access to personalized medicine at the same time that there is a presidential initiative to promote precisely these genetic tests.

"Here at Mayo, we recently conducted a study involving about 1,000 patients," stated Black. "Each study participant was genotyped for five genes (*CYP2C9, CYP2C19, CYP2D6, SLCO1B1*, and *VKORC1*).

"All of these genetic test results were put into Mayo Clinic's electronic health record system to help clinicians who would manage these patients. And, by the way, this testing was free to the patients," he added. "We found that only 20.5% of patients who had our *CYP2D6* testing did not have a variant! The remainder of those 1,000 patients—meaning 79.5%—had an issue with *CYP2D6*.

"Further, just 40.1% of these patients had no *CYP2C19* variants, leaving 59.9% with an issue," said Black. "For *CYP2C9*, 63.7% had no variants and the rest had issues. This tells us these are very common variants.

"When all of the variants found in our samples are added up, only 1% of those 1,000 patients had no variants for all of the genes," he continued. "The remaining 99% had some genetic variants, which might impact their care depending upon which medications they will need in the future.

"Now take the results of this study and view the findings as a health insurer would view them," suggested Black. "An insurer

may state that, 'If only 1% of patients were normal across the board, this would indicate that everyone needs this testing before prescribing these drugs. But our health plan cannot afford that.' This is what is happening when Medicare says it won't pay for these genetic tests. It is reacting to the costs.

"When you pick a population at risk, what is the collective value of this testing?" asked Black. "To answer that question, you have to ignore the concerns of the individual patient whose stent will close because he/she got the wrong drug. Or a patient will have a major heart attack.

"So, insurers are asking, 'What was the cost of treating that patient versus the cost of pharmacogenomic testing?'" noted Black. "Apparently, what insurers see—at least at this moment—is that this genetic testing doesn't pencil out from a financial perspective.

Collecting Data For Coverage

"Now that we have the results of the five gene-panel analysis on 1,000 patients, we're considering expanding that work to 10,000 Mayo Clinic patients," he said. "We would follow them and try to produce numbers to show insurers that this testing could be reasonable to cover.

"We feel it's important to put the patient at the center of the entire medical discussion and back that position with big dollars," noted Black. "I don't know exactly how much was spent to run the five gene-panel test for the study. We also have a nine-gene panel that we offer internally here, and when we run that test, those results go into the patients' medical records so that the results are available for their future care.

"It's important to note that Mayo Clinic is not the only medical center doing this type of testing," concluded Black. "Others are doing some proactive testing so that they will have those results for their patients for years to come." TDR

—Joseph Burns

Tamoxifen, Codeine Have A Useful CYP Gene Test

TAMOXIFEN IS ONE OF THE MOST COMMON MEDICATIONS for which physicians use pharmacogenomic testing of *CYP2D6* to assess how well a patient will metabolize the medication.

"The test for *CYP2D6* assesses for responsiveness to tamoxifen, an agent used to prevent breast cancer reoccurrence. *CYP2D6* turns tamoxifen on," said John Logan Black, III, MD, Co-Director of the Personalized Genomics Laboratory at Mayo Clinic. "So, it's very important to know how the patient will respond or if the patient will respond to tamoxifen therapy.

"For women who are prescribed tamoxifen, some will get tamoxifen and have a recurrence of breast cancer because of the way they metabolize the medication," he added. "These women would have better outcomes if the genetic testing were done and they didn't have a recurrence of breast cancers.

"One drug for which the *CYP2D6* test is even more important is codeine, a very common analgesic," he stated. "If the patient metabolizes codeine poorly, then it is like taking water. It won't help the patient. But if the patient is an ultra-rapid metabolizer and takes the typical dose of codeine, the patient may overdose because the patient converts codeine to morphine too rapidly. Some patients will hallucinate, and others may have respiratory depression. Pediatric patients appear to be at particular risk.

"Many medical centers will genotype all pediatric patients upon admission to look for *CYP2D6* variants," noted Black. "Or, most medical centers have decided not to use codeine because of this risk. So, for codeine, the results of this pharmacogenomic testing are very significant."

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Regulatory Update

Are Clinical Labs and MACs Ready to Implement ICD-10?

ALCA expresses concern that Medicare contractors may use ICD-10 as a way to limit payment under some local coverage determinations

ARE CLINICAL LABORATORIES and pathology groups prepared for ICD-10? Or, perhaps a better question to ask is this: Are Medicare Administrative Contractors prepared to switch to ICD-10 on October 1?

A recent survey of clinical laboratories and pathology groups by **McKesson Corporation** showed that 18% of respondents were unprepared for the transition to the more complex coding set for ICD-10. Further, 31% were only partly ready for the transition. The remainder were prepared, McKesson data show.

The total of 49% of labs and pathology groups that were not quite fully ready is worrisome because unprepared provider organizations may not get paid until they make the transition to ICD-10. Experts recommend that providers set aside three to six months of cash as a reserve in case payments stop because the lab, health plan, or MAC is unprepared to process claims using ICD-10.

While MACs may be ready to process claims using ICD-10, the **American Clinical Laboratory Association** wrote a letter to the federal **Centers for Medicare & Medicaid Services** last month to point out that many of the MACs' local coverage determinations were incompatible with ICD-10.

After reviewing several LCDs, JoAnne Glisson, the ACLA's Senior Vice President, wrote to officials at CMS saying, "We have found that several of the future LCDs do not include the full range of ICD-10 codes that map to the ICD-9 codes in the current policies. This may result in non-coverage for some currently-covered laboratory services, without the benefit of comment and notice periods, and it also may result in laboratories having to code improperly in some cases to be paid for their services."

Will MACs Limit Coverage?

There could be many reasons that some MACs did not use the ICD-10 mapping tools, she added. "In any event, we are concerned about the operational and claims processing effects of contractors' coding decisions," she wrote.

ACLA is concerned because the MACs may use the transition to ICD-10 to limit coverage for clinical laboratory services without allowing labs to comment, wrote Glisson. "We believe that all MACs should be required to use a notice-and-comment process if they intend to limit the indications for which certain tests are considered medically necessary," her letter said. ACLA requested a meeting with federal officials to discuss these concerns.

In addition to setting aside at least three months of cash reserves, experts recommend that providers contact all vendors and business partners to ensure that they are ready to comply with the ICD-10 coding requirements. These vendors and partners include health plans, federal and state payers, clearinghouses, and any labs that serve as vendors or business partners. TDR

Compliance Update

OIG Says It Is Ready to Target Physicians in Kickback Cases

OIG's new fraud alert targets doctors, saying both parties in fraud/kickback schemes will be charged

PHYSICIANS WHO PARTICIPATE IN schemes that violate anti-kickback and fraud statutes will be at greater risk of prosecution by federal healthcare officials. This development comes following the June 9 release by the OIG of "Fraud Alert: Physician Compensation Arrangements May Result in Significant Liability."

This new fraud alert signals a shift by the OIG to charge both parties in any fraud or kickback scheme, according to the law firm **King & Spalding** in Atlanta. To give this fraud alert more teeth, it was disclosed by *Modern Healthcare* that the Office of Inspector General (OIG) at the federal **Department of Health and Human Services** is hiring additional attorneys to combat healthcare fraud.

Pathologists and lab administrators across the nation will be watching to see if the OIG does, in fact, begin to investigate and bring charges with more frequency and vigor against physicians who accept kickbacks and other forms of inducements from clinical laboratory companies.

Doctors Now Have More Risk

It has been pointed out regularly over the past two decades that, if federal officials do not regularly bring cases against physicians who accept kickbacks from laboratories willing to push compliance with federal and state laws, then physicians have no reason to fear consequences from accepting the various forms of kickbacks and inducements offered by lab companies willing to bend the rules in their favor.

The Anti-Kickback Statute allows prosecutors to file criminal charges against both parties in a kickback arrangement, King & Spalding explained. In general, however, the OIG has not pursued criminal charges against physicians receiving kickbacks, K&S said. Instead, investigators have focused on the party paying the kickback, the law firm added.

Prosecutors Will Target Docs

The fraud alert and recent actions in which federal prosecutors brought criminal charges against doctors receiving kickback payments demonstrates a shift in that stance. There was at least one recent case where physicians accepting kickbacks from laboratory companies have been investigated and charged under federal law.

For physicians, the fraud alert sends a strong message, stated **Alston + Bird**, a law firm in Washington, D.C., that does a significant amount of work for clinical laboratories. The firm's attorneys wrote that the alert underscores OIG's focus on doctors who have questionable compensation arrangements with provider organizations. These include hospitals, nursing homes, dialysis clinics, and similar providers, Alston + Bird said. The law firm did not mention clinical laboratories or pathology groups specifically.

"The OIG is increasingly scrutinizing such arrangements to ensure that they reflect fair market value for bona fide services and otherwise comply with the federal anti-kickback statute (AKS),"

Alston + Bird said. "Indeed, the OIG revealed in the fraud alert that it recently reached settlements with 12 physicians who received compensation under medical directorship agreements that did not reflect fair market value for the services to be performed," the law firm commented.

"In some instances, the institutional provider also paid the salaries of the physicians' front office staff, which the OIG found to constitute improper remuneration," the law firm added.

Bio-Diagnostics Lab Case

In an investigation into kickbacks given to physicians, federal prosecutors working on the case involving **Biodiagnostics Laboratory Services, LLC**, in Parsippany, New Jersey, filed charges against 25 doctors, 12 of whom have been sentenced. Some of the doctors got probation but some got prison terms. The *Bergen Record* reported that 38 defendants have been charged, including "25 doctors from New Jersey, New York and Connecticut, in what is believed to be one of the largest—if not the largest—laboratory bribery prosecutions in the United States, both in terms of money and the number of physicians caught with their hands out."

Another recent case of fraud involving medical laboratories is still under active investigation. Earlier this year, **Health Diagnostic Laboratories** of Richmond, Virginia, and **Singulex** of Alameda, California, settled a federal case involving multiple whistleblowers. Both companies denied the allegations in the *qui tam* case, while agreeing to pay restitution under the settlement agreements. *(See TDR, April 20, 2015.)*

When the settlement agreements were announced, officials at the Department of Justice revealed the existence of additional legal cases against executives of HDL, a lab marketing company, and another laboratory. Legal experts believe that the U.S. attorneys handling these cases are continuing to investigate these cases and that, along with lab executives, physicians who accepted payments considered to be kickbacks may also face federal charges. TDR

OIG Signals its Intent To Be Tougher on Doctors

KICKBACKS AND ILLEGAL INDUCEMENTS clinical laboratory companies paid to physicians have been prominent elements in two legal cases pursued by the Department of Justice in recent years. Some legal experts believe these two cases were a factor in the decision by the Office of the Inspector General of the Department of Health and Human Services to release a new fraud alert on June 9.

Titled, "Fraud Alert: Physician Compensation Arrangements May Result in Significant Liability," the document describes the following as a potential kickback:

> *Physicians who enter into compensation arrangements such as medical directorships must ensure that those arrangements reflect fair market value for bona fide services the physicians actually provide. Although many compensation arrangements are legitimate, a compensation arrangement may violate the anti-kickback statute if even one purpose of the arrangement is to compensate a physician for his or her past or future referrals of federal health care program business. OIG encourages physicians to carefully consider the terms and conditions of medical directorships and other compensation arrangements before entering into them.*

It is noteworthy that, along with issuing this OIG fraud alert, federal officials called attention to the fact that the OIG was hiring additional lawyers to combat healthcare fraud. Not in two decades have federal agencies issued such clear warnings for physicians to stear clear of arrangements that might be viewed as involving kickbacks or illegal inducements.

INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

Turf wars are breaking out among local pathology groups as consolidation involving hospitals and physicians' practices continues to reshape many regional healthcare markets. The latest sign of this trend comes from Washington State, where **CellNetix** of Seattle announced an agreement to provide anatomic pathology and molecular diagnostic services to **Rockwood Health Services** of Spokane. This puts CellNetix, with 50 pathologists, right in the backyard of Spokane-based **Incyte Diagnostics** and its 44 pathologists. Rockwood Health Systems includes 307-bed **Deaconess Hospital**, 123-bed **Valley Hospital**, the **Rockwood Clinic** and affiliated medical groups and providers.

MORE ON: *Pathology consolidation*

In another pathology transaction that represents ongoing consolidation within the anatomic pathology profession, **Summit Pathology** (with 11 pathologists) of Loveland, Colorado, will acquire **AnaPath Diagnostics Inc.** (currently with three pathologists), of Cheyenne, Wyoming. The acquisition will broaden the geographical reach of Summit Pathology and is typical of smaller pathology group practice mergers that happen quietly and with little public notice.

SONIC ACQUIRES BIG SWISS LAB

Sonic Healthcare Ltd., of Sydney, Australia, has agreed to pay US$300 million to buy **MediSupport SA** of Morges, Switzerland. When closed, the purchase will make Sonic the largest lab company in Switzerland. MediSupport employs 700 people and operates facilities in 10 Swiss cities. It is a major provider of genetic tests and gene sequencing services.

TRANSITIONS

• **Baylor Miraca Genetics Laboratories, LLC,** of Dallas, Texas, announced that Gary Huff will be its new President and CEO. Huff has held executive positions at **Solstas Lab Partners, Affinity Solutions International, Inc.**, and **Laboratory Corporation of America**.

• Barbara Blasutta will retire on July 3 from her position as Vice President, Operations, Hospital Laboratories at **Laboratory Sciences of Arizona** and **Sonora Quest Laboratories**, based in Phoenix, Arizona. Blasetta started at **Sonora Laboratory Services** in 1992.

DARK Daily
Clinical Laboratory and Pathology News/Trends

DARK DAILY UPDATE

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

...the findings in *Medscape*'s "Physician Compensation Report for 2015." For pathologists, average compensation of $267,000 in 2015 ranked them below the average of $282,000 for the 25 specialties included in the survey.

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

That's all the insider intelligence for this report. Look for the next briefing on Monday, July 13, 2015.