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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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R. Lewis Dark

Founder & Publisher

Medicare's New Policy May Help Labs

ONCE AGAIN, **THE DARK REPORT** IS FIRST TO ALERT YOU to a significant development in the laboratory testing marketplace. I am referring to a new and evolving Medicare policy which calls for the agency to reimburse for expensive new medical treatments and diagnostic tests.

As you will read on pages 14-15, this policy has two conditions. First, companies or organizations must do research studies to determine the clinical effectiveness of these new medical and diagnostic procedures. Second, patients receiving these treatments must agree to participate in the research studies.

I have two reasons to consider this to be an exciting development—one that is most auspicious for the laboratory testing industry. My first reason is the obvious link between an expensive new laboratory test, and the relatively small cost (when compared to new therapeutic drugs, for example), to demonstrate its clinical relevance. Medicare is creating an economic motive for companies which develop these tests to fund the research studies and demonstrate whether or not there is a clear clinical benefit.

It is my second reason which holds even greater promise. I believe this Medicare policy is the direct result of a different political philosophy which is infiltrating many government bureaucracies. That philosophy is to use market incentives to drive improvement and progress. Medicare is reversing a 38-year pattern of arbitrarily granting or denying reimbursement for new medical technologies. Instead of standing as gatekeeper and supporting the status quo, Medicare is now taking active steps to get companies, disease-specific associations, and medical specialty organizations to step forward—with their own dollars—to track Medicare patients and perform rigorous outcome studies on those who receive these new treatments and diagnostic tests.

For pathologists and lab administrators, this is an ideal situation. It means payment for new diagnostic tests ordered by clinicians, along with a role in supporting the research studies needed to validate the clinical performance of both new medical treatments and new diagnostic tests. For my part, I hope we see more such innovative policies by government healthcare policy-makers. It's time to move away from the old Soviet Union-style command and control system and let doctors and their patients make choices driven by market realities. TDR

Big Seattle Med Center Adopts "Lean" Methods

Hospital administrators travel to Japan for first-hand study of Lean techniques

CEO SUMMARY: Laboratory and pathology services at Virginia Mason Medical Center are an integral part of its hospital-wide Lean quality management initiative. Because of the importance of lab test data to so many clinical services, the laboratory often finds itself making key contributions in the process improvement efforts mounted by such clinical services as the emergency department and outpatient clinics.

IN SEATTLE, WASHINGTON, **Virginia Mason Medical Center (VMMC)** is one of the nation's first hospitals to fully embrace both the philosophy and techniques of Lean quality management methods.

But there is another unusual twist in the VMMC story. To help administrators, managers, physicians, and nurses better learn how to effectively use Lean methods, VMMC has regularly sent teams to Japan. During these trips, VMMC's staff get to see, first-hand, how Lean techniques are used in some of the world's best-run manufacturing plants and businesses.

During the past year, THE DARK REPORT provided early intelligence about how the laboratories in three major hospitals/health systems became first in the nation to use Lean to re-engineer the work processes in their high-volume core chemistry and hematology laboratories. *(See TDR, September 8, 2003.)* The three labs each posted gains of 50% or more in key measures as a result of their Lean "make overs," which generally took only 14 weeks to accomplish.

Within the hospital industry, Virginia Mason Medical Center (336 beds) is an early-adopter. Its decision to make Lean the primary management philosophy throughout the organization sets it apart even from the handful of hospitals known to have chosen Six Sigma management systems to underpin their evolution into the next generation of quality management.

Both the clinical lab and the anatomic pathology department at VMMC are

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engaged in learning and applying Lean management methods. What is distinctive about their experience with Lean to date is that the laboratory and the pathology departments participate in the multidisciplinary Lean teams. For this reason, VMMC provides an early look at ways in which a hospital-wide quality management transformation will change many long-standing aspects of laboratory and pathology support services.

Implementing Lean

"Lean is transforming our hospital organization and the way all of us view our work processes," stated Lee Darrow, Administrative Director of Laboratories at VMMC. "Lean techniques consistently allow us to streamline and refine work processes that cross several departments within the hospital. As multiple departments get involved in these projects, long-standing divisions melt away, replaced by effective collaboration. Lean can be both energizing and empowering."

In an exclusive interview with THE DARK REPORT, Darrow explained how VMMC has deployed Lean techniques within the hospital. "We use what are called 'Rapid Process Improvement (RPI) Workshops.' These focus our quality efforts by concentrating all the necessary resources into a one-week session," she explained.

"The organization of an RPIW is simple and consistent," explained Darrow. "There are four to five weeks of data gathering and preparation prior to the actual week-long session. Day one is devoted to teaching Lean techniques and giving the work team data and targets. During days two, three, and four, the team studies their data and moves to the gemba (shop floor) to apply solutions that enable them to achieve their targets. Implementation of solutions involves all departments and service areas of the hospital necessary to effect the change.

"On Friday morning, day five, the RPIW team reports its findings and actions in a meeting that is open to everyone, from the top administrators, and clinicians to line staff," she noted. "Any implementation work remaining is continued and reported in a system-wide newspaper. The full implementation is expected to be completed within 30 days following the end of that RPIW. Follow-up data is collected at 30, 60, and 90 days to insure that all gains made as a result of the RPIW are sustained."

VMMC's Lean journey began in June 2002, when the first group of senior administrators and board members traveled to Japan. Upon their return, the commitment was made to implement Lean management methods throughout the hospital, its affiliated clinic sites, and other facilities.

"During the second half of 2002, there were six Rapid Process Improvement Workshops," stated Darrow. "Lean training commenced throughout the organization. In 2003, the number of RPIWs increased steadily. Today, 100% of our 5,000 employees are familiar with Lean. There are an average of three to four RPIWs each week. This level of activity is generating a steady stream of improvements and changes to work processes in every aspect of our health system's operations."

Trip To Japan in 2003

Darrow was on the team which visited Japan in June 2003. "It was a two-week trip that was eye-opening. We visited only industrial facilities and did not go into any healthcare organizations," she recalled. "I was most impressed with the Japanese emphasis on quality and safety. We were taught to 'look with our eyes', but to 'see with our hands.' It is an important part of the Lean process to interact directly with the work processes themselves. In other words, to 'get

How Lean Came to Virginia Mason

IT WAS A CHANCE ENCOUNTER on an airplane in 2001 that introduced the President of Virginia Mason Medical Center (VMMC) to how Lean quality management methods could improve the quality of services in his hospital and affiliated clinics.

VMMC President Michael Rona found himself seated next to John Black, who is President of **John Black and Associates, LLC/Shingijutsu America, LLC**. This company is the American arm of Shingijutsu, a leading Japanese Lean consulting company. Upon his return to Seattle, Rona shared this new knowledge with VMMC Chairman and CEO Gary S. Kaplan, M.D. Both men were quick to act. The decision was made to engage Black/Shingijutsu to help VMMC implement a Lean program.

"We knew the status quo methods were not working," stated Kaplan in a published interview. "Even with a strong culture of teamwork, it would be difficult to make rapid changes to improve the patient experience without the new [Lean] methods and new tools discovered through what is now called the Virginia Mason Production System."

Kaplan was hoping to accelerate the time required to realize quality improvements—and do it in such a way that improvements would be strongly embedded and not subject to unraveling or backsliding in subsequent months. He also wanted to move past incremental improvements that took months and create a system that achieved breakthrough results in hours.

"One of the things we're doing is beginning to think of our work in terms of service lines," Kaplan noted. "We're looking at aligning our metrics and our measuring tools around service-line performance."

dirty' and be part of the actual work process under review.

"During part of my visit, we worked eight- and ten-hour days on the factory floor of an air conditioning factory that has practiced Lean for years. We also visited **Toyota** and saw the unprecedented results of 50 years of Lean methods," she said. "It was an intense learning process and made us realize how much we could improve our work processes at VMMC."

First Lab/Pathology RPIW

Back in 2002, VMMC's first series of rapid process improvement workshops targeted improvements in surgery. It was a multi-disciplinary effort. "Before my trip to Japan in June 2003, we made a value stream map of surgical pathology," stated Darrow. "Also on the trip was Christina Isaacson, M.D., Deputy Chief of Pathology. After our return, in August 2003, we conducted an RPIW focused on surgical pathology.

"This RPIW had several goals," she continued. "We wanted to reduce defects [errors] in surgical pathology, reduce transcription time, and speed up the flow of specimens in histology. The outcomes from this RPIW were impressive.

"First, we reduced specimen labeling errors by 52% and cassette labeling errors by 73%. The removal of non-urgent outpatient cases from the busy—and often chaotic—inpatient surgical pathology lab allowed us to slash lead times for gross dictation of outpatient surgical specimens by 67%! A similar work flow redesign cut our dictation lead time for inpatient surgical specimens by 49%," observed Darrow.

Surgical Pathology Project

"I should also add that this surgical path RPIW was done in conjunction with efforts to improve work processes in our surgery suites," she added. "VMMC's Lean process takes a wide view across

all disciplines which affect the primary subject of an RPIW."

An example of the "wide view" perspective is an early RPIW which targeted how to improve the patients' experience when they visited outpatient clinics affiliated with VMMC. In looking to improve clinical outcomes and patient safety while also increasing patient satisfaction, the project team identified turnaround time for lab test reporting as a key influence.

Patients Are Part of RPIWs

This RPIW included patients, which happens frequently at VMMC. One outcome of this project is that the actual time it took to report test results back to patients was reduced by 85%. This project also identified the importance of having certain test results available to the physician at the time of the patient's appointment, such as a diabetic patient's hemoglobin A1C test results at the time of the physician visit.

"The laboratory has done a number of RPIWs," said Darrow. "One focused on phlebotomy services. By utilizing single piece work flow in our system, we cut average wait times for outpatient phlebotomy during peak times from 45 minutes to an average of under 10 minutes. This also cut the number of patients waiting in the phlebotomy reception area by 55%.

"RPIWs have also been done for the clinical laboratory," she continued. "A project in hematology addressed work flow and safety issues. We removed fixed counters and reconfigured the work cell into a U-shape. This freed up 486 square feet of lab space and allowed us to move the cell marker laboratory into hematology. Staff walking distance in hematology was reduced by 62%. We now also can float staff between hematology and cell markers in response to fluctuations in workflow."

Lean Methods Allow Focus On Four Key Strategies

UNDER the Virginia Mason Production System, Lean methods allowed the institution to replace 15 strategies that described how it would achieve its goals with just four strategies, listed below:

1. Recruiting and retaining the best people.
2. Relentlessly pursuing the highest quality outcomes of care.
3. Unequivocally insisting on extraordinary patient service.
4. Promoting a culture of innovation.

Darrow's lab is regularly involved in RPIWs focused on other hospital services. "Not surprisingly, we are often asked to use our LIS to create additional processes that will speed up delivery of test results to physicians. We also reduced turnaround times to support preoperative testing and emergency department lab testing needs."

The Laboratory's Role

Such demands upon the laboratory are consistent with its role as the "information factory" for the hospital and its affiliated clinics. THE DARK REPORT believes this is a logical outcome for a hospital-wide Lean quality management program, since laboratory test data is critical to the hospital's clinical mission.

Virginia Mason Medical Center's experience in deploying Lean techniques reinforces the importance of lab medicine to the institution's mission of high quality outcomes, improved patient safety, and increased patient satisfaction—not to mention lower costs per healthcare encounter because of better quality inside and outside the lab. TDR

Contact Lee Darrow at 206-223-6850.

CA, FL, BC Move Forward With Lab Test Contracts

Government health programs push plans to issue restrictive lab testing contracts

CEO SUMMARY: Medicaid agencies in the bellwether states of California and Florida continue to push ahead with plans to revise laboratory test contract policies. In British Columbia, private laboratory companies face an uncertain future as the provincial health administration maneuvers to upset the laboratory contracting status quo. It's a trend with the potential to be emulated by other state Medicaid programs.

GOVERNMENT HEALTH PROGRAMS in three regions continue to push changes that alter long-standing policies governing which laboratories can provide testing services to government-insured beneficiaries.

In California, the Medi-Cal program wants laboratories to apply for a contract that grants them access to provide testing services to Medi-Cal beneficiaries. Laboratories which do not hold such a contract will be unable to submit reimbursement claims for Medi-Cal patients. *(See TDR, May 17, 2004.)*

Statewide Contract In FL

In Florida, despite much controversy, the **Agency for Health Care Administration** (AHCA) continues with its plans to conduct an RFP process and award one laboratory with a three-year contract to provide outpatient laboratory testing for all Medicaid patients in the entire state. *(See TDR, April 26, 2004.)*

Across the border in the Canadian province of British Columbia (BC), the provincial health administration still holds trump cards in its stated goal to competitively bid outpatient laboratory testing. In reaction to the original proposal, the **British Columbia Medical Association** (BCMA) raised significant objections. The resulting compromise seems unsatisfactory to all parties and the competitive bidding initiative might still occur. *(See TDR, April 26, 2004.)*

The significance of these three radical contracting initiatives is simple. Historically, government health plans have been open to all laboratory providers holding proper licenses and operating in a responsible manner. Now, in parallel, government health program authorities in California, Florida, and British Columbia are taking aggressive steps to effectively limit the number of laboratories allowed to serve government-insured beneficiaries. Any success they have in reducing the cost of laboratory testing services will encourage other state Medicaid programs to initiate similarly restrictive laboratory contracting schemes.

"In California, the deadline for laboratories to submit their response to the Medi-Cal RFA (Request for Application) is November 29," stated Michael Arnold, Legislative Advocate for the **California Clinical Laboratory Association** (CCLA). "Approximately 400 free-standing laboratories in the state received the RFA. Once Medi-Cal evaluates these applications and selects its contract laboratories, any laboratory that does not hold a contract will be excluded from doing lab tests for Medi-Cal patients.

Evaluating Applications

"The contract process was drafted in such a way that it appears a laboratory which meets minimum criteria will be accepted," he explained. "But because this is the first contract cycle, no one can really predict how Medi-Cal will score these responses and award contracts."

Arnold believes that the Medi-Cal laboratory test contracting initiative will radically change another facet of the laboratory marketplace in California. "Each laboratory which applies must document its compliance programs. In signing its Medi-Cal contract, it is agreeing to fully comply with all terms of the contract. If the Medi-Cal agency decides the laboratory is in breach, it can void the contract and exclude the laboratory as a Medi-Cal provider," he said.

Shifts Burden Of Proof

"This reverses the current situation, where the burden of proof is on Medi-Cal whenever it wants to exclude a laboratory provider for cause," added Arnold. "These new contracts place the burden of proof on the laboratory to demonstrate that it is in compliance with all contract terms—after Medi-Cal has declared it in violation of the contract and then excluded it as a contract provider of laboratory tests to the Medi-Cal program."

In Florida, the situation is less clear. Earlier this year, AHCA, which administers the state's Medicaid program, launched an RFP process that would select a single laboratory to provide all outpatient laboratory testing for the state's Medicaid patients for a three-year period. The estimated total value of this contract is $100 million. AHCA declared that the contract process was needed to fulfill a legislative mandate passed the previous year.

"Medi-Cal's RFA proposal is already changing the competitive market for lab services in California."
—Michael Arnold

This restrictive contract triggered howls of protest, not just from labs, but also from influential employer groups like the **Florida Healthcare Coalition**. There were obvious flaws in the design and timing of AHCA's RFP process. Faced with intense criticism, AHCA withdrew the original RFP, but announced its intention to meet the legislative mandate for competitive bidding by issuing an Invitation to Bid (ITN). As of press time, AHCA has not provided a firm date for issuing the ITN nor a revised timeline for the contract award process.

In discussions with several individuals knowledgeable about different aspects of the Florida situation, THE DARK REPORT has uncovered an interesting fact. The state law to which AHCA is responding with the sole-source Medicaid lab services contract has another provision covering Medicaid laboratory testing.

This law specifies that, if AHCA has not implemented an initiative which generates a targeted reduction in the cost of laboratory testing by April 2005, two changes are to be implemented. The first

change is an arbitrary reduction of 10% in laboratory testing fees paid by the Florida Medicaid program. The second is a requirement that labs providing testing services to Medicaid must transmit test results electronically to an Internet-based pharmacy-ordering system.

Individuals in Florida tell THE DARK REPORT that, within AHCA, the scheme to grant a single laboratory an exclusive, statewide contract for three years has become a "monster." No bureaucrat apparently wants to be associated with this project.

"Do Nothing" Strategy

Informed sources believe that AHCA's inactivity on this issue is significant. They speculate that, with April 2005 less than five months away, AHCA's strategy may just be to let the proposed RFP lay dormant. After that date, it is a less complicated process to institute the 10% reduction in laboratory test reimbursement and establish a timeline for laboratories to comply with the electronic reporting requirement.

One reason why this scenario may play out is that the Florida Medicaid program would like to find a way to exclude smaller labs it considers most likely to be of lesser quality and most susceptible to fraudulent billing practices. The cost of implementing an electronic reporting capability will be a prohibitive expense for many of those smaller laboratories.

Better Than The Alternative

A default result in April 2005 would probably be welcomed by most laboratories in Florida. When compared to losing access to Medicaid patients because of an exclusive contract given to one laboratory, this would be a more palatable outcome.

For private laboratory companies in British Columbia, much uncertainty remains about the eventual outcome in their opposition to the **Ministry of**

Competitive Bidding In Medicare Program

COMPETITIVE BIDDING for lab testing service is a concept that holds allure for government health program officials. That's because it has the potential to generate a significant reduction in the cost of that care—albeit at the expense of laboratories which perform those tests.

Similar to competitive bidding efforts in Florida and British Columbia, the Medicare program has announced the details of a competitive bidding demonstration involving laboratory testing services. Congressional legislation passed last year mandates this demonstration project and calls for an initial report back to Congress on the results of the demonstration "not later than December 31, 2005."

This latest interest in competitive bidding was stimulated by the results of a competitive bidding demonstration project involving durable medical equipment (DME). Conducted in Polk County, Florida and San Antonio, Texas, this project generated savings to Medicare of 17% and 22%, respectively. In response, Congress has directed Medicare to expand competitive bidding for DME.

To enable the demonstration project involving laboratory testing services, the **Centers for Medicare and Medicaid Services** (CMS) awarded a contract to **RTI International** and its subcontractor, **Palmetto GBA, LLC**. The contract award was announced on September 30, 2004.

RTI, based in Research Triangle Park, North Carolina, is a not-for-profit corporation that specializes in scientific research and technology development. As one example of its activities, RTI International will compile the information used by *U.S. News & World Report* to report its annual "America's Best Hospitals" rankings for 2005.

Health's stated plan to institute competitive bidding. The mischief was started when a "Lab Reform" initiative was developed in early 2003.

This began with a law that specified cuts of 8% and 12% to laboratory test fees were to be enacted by September 1, 2003 and April 1, 2004, respectively. The other major damaging element of the regulation was the introduction of a competitive bidding program for laboratory testing services in British Columbia.

Physicians Were Alarmed

"There was considerable concern that this 'Lab Reform' regulation was an attempt to push private laboratory providers out of the BC health system," stated Douglas Buchanan, CEO and Managing Director of **BC Biomedical Laboratories, Inc.**, based in Surrey, British Columbia. "These proposals alarmed many physicians in the province. They registered their opposition in several ways, including a court challenge."

That earned a notable victory in a hearing at the Supreme Court of British Columbia. The court ruled that the executive branch of government had overstepped its authority in issuing the "Lab Reform" regulations. The court declared them illegal. Following this ruling, the government and BCMA finally sat down to work out an interim one-year working agreement

Agreed To Fee Cuts of 20%

"Under the agreement, laboratories accepted a 20% reduction in reimbursement, effective April 1, 2004," explained Buchanan. "To identify alternative ways to reduce the cost of laboratory services, a number of investigative task forces were formed.

"Each task force is made up of representatives from the government, physicians, laboratories, and other stakeholders," he continued. "They are reviewing lab fees procedure by procedure, looking at lab test utilization, exploring the benefits of information integration, and other ideas.

"These task forces must report their findings in coming months. Until then, the government cannot implement competitive bidding for lab testing services. However, there is no certainty that the government will agree to implement the task forces' cost-saving recommendations in lieu of proceeding with competitive bidding. It remains an unsettling situation," observed Buchanan.

THE DARK REPORT considers events in these three regions as warning signs of a growing threat to the laboratory industry. Government health plans, faced with a funding crisis, will take ever more extreme steps to save money.

Govt. Contracting Strategy

It is no coincidence that government health program authorities in California, Florida, and British Columbia have initiated radical measures in how they contract for laboratory services. Each of these regions is known as progressive and innovative in the evolution of their government health programs.

Another factor may further encourage state Medicaid agencies to use these types of laboratory contracting schemes to reduce what they pay for laboratory tests. That is Medicare's impending competitive bidding demonstration program for laboratory test services. *(See sidebar on previous page.)* Should this Medicare demonstration project result in significantly lower costs for laboratory tests, expect more state Medicaid programs to follow the same path. TDR

Contact Michael Arnold at 916-446-2646 and Douglas Buchanan at 604-507-5120.

HPV Vaccine Developers Racing to Marketplace

Merck and GlaxoSmithKline both hope to be first to win approval from regulators

CEO SUMMARY: At least ten companies are working on an HPV vaccine that can prevent cervical cancer. The leading two companies have Phase III clinical trials under way and expect to earn regulatory approval within the next 24 to 30 months. The speedy arrival of an HPV vaccine in the market will not affect Pap smear testing volumes—in the short term. But it lays the groundwork for substantial long term change.

FOR THE LABORATORY INDUSTRY, development of an effective vaccine for Human Papillomavirus (HPV) is probably a financial good news/bad news story.

The good news is that, even following regulatory approval of an effective HPV vaccine, current cervical screening guidelines are unlikely to change for at least a decade. Moreover, the need to run a diagnostic test for HPV will increase the volumes of such tests performed annually in this country.

The bad news is that widespread vaccination of vulnerable populations will spell the end of Pap smear testing as it is practiced today. In the United States, that will mean a substantial reduction in the estimated 55 million Pap smears currently performed each year.

Many lab directors and pathologists saw headlines earlier this month reporting the results of human HPV vaccine trials. The findings were presented at a recent meeting of the **American Society for Microbiology** (ASM). Researchers at the **University of Washington** reported the results of this study, which was funded by **Merck & Co.** The study involved 755 women who had been part of an earlier HPV vaccine study. After their vaccination for HPV-16, these women were followed for a total of four years.

During this time, seven women became infected with HPV-16, but none developed pre-cancers. In the control group, 750 women received placebo shots and 111 became infected with HPV-16. Twelve women in this group formed pre-cancers.

HPV Vaccine Trials

Merck is one of two major pharmaceutical companies racing to be first to earn regulatory approval to market their HPV vaccine. Merck is in the final stages of testing an expanded vaccine that would protect against HPV strains 16, 18, 6, and 11. These four strains cause about 70% of all cervical cancers. About 90% of genital warts cases in men and women are also caused by these HPV strains.

Merck's Phase III clinical trial is now underway, involving 25,000 men and

Eat a Banana, Vaccinate Against the HPV Virus

EVEN AS RESEARCHERS RACE TO DEVELOP an effective vaccine for HPV, a parallel research effort is under way to develop an edible vaccine against the same disease.

Edible vaccine research is ongoing at the **University of Rochester**, **Cornell University**, and **Tulane University**. Two years ago, researchers developed a genetically-altered potato that stimulated an immune response in mice.

The goal is to create an oral vaccine that eliminates needles. "The beauty of an oral vaccine is that you don't need a needle," observed Robert Rose, Ph.D., a virologist involved in this research project at the **University of Rochester** in Rochester, New York. "You don't need sterile injection equipment or highly-skilled medical personnel who know how to inject a vaccine. You just need to put a couple of drops on someone's tongue. Part of the reason that polio has been virtually stamped out is because of development of an oral vaccine."

HPV is not the only oral vaccine target for this research. Other diseases include hepatitis B, rotavirus, tooth decay, and respiratory syncytial virus. Potential foods that could deliver an oral virus are bananas, potatoes, and apples.

The work centers around VLPs—virus-like particles. These look like viral particles, but are not infectious. VLPs can trigger an immune response by the body. Researchers use genetic splicing techniques to insert VLPs into plants. As a plant grows, it then produces VLPs in its fruit and leaves.

Rose says that the banana is a preferred food. Because heat often destroys protein, a food that is eaten uncooked and is tasty, such as a banana, is preferred as the delivery vehicle for vaccines that can protect against HPV and other diseases.

women located in 34 countries. It expects the results of this study by mid-2005.

Sometime in the second half of 2005, Merck expects to submit an application for its quadrivalent HPV vaccine with the **Food and Drug Administration** (FDA). If approved without unexpected delays, Merck believes it will be first to market with an HPV vaccine.

GlaxoSmithKline's Progress

Merck's closest competitor is **GlaxoSmithKline (GSK) Plc**. It is developing its own HPV vaccine in collaboration with **Medimmune, Inc.** of Gathersburg, Maryland.

Studies of its two-strain HPV vaccine (HPV-16 and HPV-18) have involved about 1,100 women, ranging in age from 15 to 25 and living in 14 countries, including the United States, Canada, and Brazil. GSK is currently launching a Phase III trial that involves 25,000 women. It calls its vaccine "Cervarix."

It had originally intended to file for regulatory approval in 2008. But, armed with favorable data from its clinical studies and feeling the pressure from Merck, GlaxoSmithKline recently announced that it was pushing up the probable filing date to 2006.

30 Months to Market

Assuming that both companies meet their announced timetables and regulators act with some dispatch, it is possible that HPV vaccines will be approved and available for clinical use within 24 to 30 months. However, the availability of HPV vaccines will not have much impact on Pap smear testing volumes for several years. That's because it will take considerable time to inoculate enough people to statistically impact the rates of infection.

"If they started vaccinating only young people before the start of sexual activity, it would be about three to four decades before you saw major

Many Companies Developing HPV Vaccines

BECAUSE THE MARKET FOR AN HPV VACCINE is predicted to be in the billions of dollars, many companies are working to perfect a product. Leaders in this race are Merck and GlaxoSmithKline. Both have launched Phase III trails and expect to file for regulatory approval to market their vaccines within the next 18 months.

Prophylactic vaccines

COMPANY	COMPOUND STATUS	DEVELOPMENT	ANTIGEN	HPV GENOTYPE
Merck/CSL	HPV Vaccines	Phase III	L1	16, 18, 6, 11
Medimmune/GlaxoSK	MEDI-507	Phase II	L1	11, 16, 18
Novavax/NCI	Recombinant HPV-16	Phase II	L1	
	VLP vaccine			16
BTG International	HPV vaccine	Phase I		
Berna Bio	HPV vaccine	Preclinical	L1	16
GSK/ Powderject	DNA vaccine	Preclinical		

Therapeutic vaccines

COMPANY	COMPOUND STATUS	DEVELOPMENT	ANTIGEN	HPV GENOTYPE
Stressgen / Roche E7	Hsp E7 (AIN)	Phase III	E7	
	Hsp E7 (RRP) Hsp E7 (genital warts) Hsp E7 (cervical dysplasia)	Phase III Phase II Phase III		
Zycos Inc	ZYC-101A	Phase IIb	E6, E7	16, 18
Xenova	TA-CIN & TA-HPV "prime boost" (AIN)	Phase II/on hold	L2, E6, E7	16, 18
Transgene	MVA-HPV-IL2	Phase II	E6, E7 16	16

SOURCE: Innogenetics, Gent, Belgium

changes in cervical cancer rates," stated Christopher P. Crum, M.D., Director of Women's and Perinatal Pathology at **Brigham and Women's Hospital** in Boston, Massachusetts. "But the changes would nonetheless be significant, and this would have a major impact, particularly in developing countries where you don't have the Pap smear."

Crum's opinion was mirrored by that of Anne Szareski, M.D., a Clinical Consultant at **Cancer Research UK**. She is leading clinical trials in London, England. "This vaccine is the most exciting thing in cervical cancer research because it is mainly caused by a virus—so the obvious thing to do is get a vaccine," she said. "It would have to protect against more than 70% to completely remove the need for [cervical cancer] screening. If we could get to 80% or more [protection], we could certainly stop [Pap] smears. Although we can only stop screening when we have reached the point where everyone's been vaccinated."

The HPV vaccine is given in three shots over six months. Researchers say that the vaccine would be most effective as a preventive measure if it is given to girls and young women before they become sexually active. Further, because the vaccine cannot prevent every virus that can cause disease, there would still be need to continue screening for cervical cancer. One unanswered question is how long immunity lasts and whether a

booster shot or revaccination would be necessary in later years.

The number of people infected with HPV is significant. It is believed that 50% of sexually active men and women acquire genital HPV at some point in their lives. More than 80% of women will have acquired an HPV infection by the age of 50. In the United States, it is estimated that 6.2 million people acquire genital HPV infections each year.

Most people will naturally clear their HPV infection. Women who do not clear their HPV infection are at highest risk for cervical cancer. About 15,000 new cases of cervical cancer are diagnosed annually in the United States. In this country, about 4,400 women die annually from cervical cancer and it is widely recognized that the majority of these women did not have a Pap smear in the five years prior to their diagnosis of cervical cancer.

Billion-Dollar Market

At least ten companies are known to be developing a vaccine for HPV. That's because the market potential for such a vaccine is immense. Research Analyst Tim Anderson at **Prudential Equity Group** characterizes Merck's HPV vaccine as possibly "one of the most important drugs to emerge" from a pharma company "in recent memory." He projects HPV vaccine sales of $2.3 billion in 2008, just 48 months away.

Adrian Howd, an Analyst at **ABN AMRO**, called GlaxoSmithKline's Cervarix a "sleeper" drug that has attracted little attention within the financial community. Howd believes sales of Cervarix could top $1.8 billion after it hits the marketplace in 2007.

The race to bring an HPV vaccine to market is driving two areas of science and medicine which will influence and shape laboratory testing in future years. First is the science behind developing vaccines for infectious diseases. This science centers around advances in proteomics. Researchers are learning how to create non-virulent virus-like particles (VLPs). These mimic, in important ways, the virus and stimulate an immune response in the body.

Using New Technology

Second is the new technology which enables this type of scientific approach in vaccine development. The ability to create VLPs is just one element. Researchers have a variety of tools to help them identify even subtle immune system responses and understand them.

Another dimension of the HPV vaccine development effort which can have a longer-term impact on laboratory medicine is this fact. The HPV vaccine's therapeutic value is that it prevents cervical cancer. "This is the first time we have shown that there is a vaccine that protects against the only cause of [cervical] cancer and can actually prevent 70% of all cervical cancer worldwide," declared Diane Harper, a researcher at **Dartmouth Medical School** in Hanover, New Hampshire who helped conduct one of the HPV clinical trial sites.

Vaccine To Prevent Cancer

Cancer prevention has been one effect from the use of the vaccine for Hepatitis B (HBV). This vaccine has reduced the number of people whose infections progress to liver cancer. Collectively, the HBV and HPV vaccines point to new medical strategies which aim to prevent cancer, not treat it after it is diagnosed.

If these types of vaccines are discovered to have the ability to prevent other cancers, it will certainly have an impact on anatomic pathology and cancer diagnostics. It also is an early demonstration of how proteomics may provide new ways to prevent disease. As that happens, laboratory tests will evolve to serve prevention, not detection. TDR

Medicare Changes Policy On New Med Procedures

CMS Director McClellan intends to revamp how new medical technology is accepted

CEO SUMMARY: Faced with a literal tidal wave of new medical procedures, new therapeutic drugs, and new diagnostic tests, Medicare is crafting a unique strategy. As a new clinical option reaches the market, Medicare will reimburse—but only if the patient participates in a clinical study and these studies are paid for by either vendors or research institutes. PET scan manufacturers are organizing the first such effort.

NEW MEDICAL TREATMENTS and diagnostic tests will be covered by Medicare under an innovative, but still evolving, policy.

In recent months, the **Centers for Medicare and Medicaid Services** (CMS) has announced that it would cover expensive clinical procedures and diagnostic tests, so long as two conditions were met. First, companies and organizations providing such healthcare services pay for research studies to determine whether or not these procedures indeed provide clinical benefit. Second, that patients receiving these treatments and tests agree to participate in the research studies.

New Philosophy At CMS

This new policy is directly linked to the arrival of Mark McClellan, M.D., Ph.D. as Director of the **Centers for Medicare and Medicaid Services** (CMS). McClellan was sworn in as the agency chief in March 2004, following the departure of Thomas Scully in December 2003. Prior to this position, McClellan, a board-certified internal medicine physician, was former Commissioner of the **Food and Drug Administration** (FDA). He also served on the **President's Council of Economic Advisers**. He was Deputy Assistant Secretary of the Treasury for Economic Policy during the Clinton Administration. He is currently on leave from **Stanford University** and **Stanford Medical School**, where he is Associate Professor of Economics and Associate Professor of Medicine, respectively.

This background is what makes McClellan unique as a Director of the Medicare and Medicaid programs. His public comments reveal a fundamental shift in attitude and philosophy. Whereas CMS (formerly HCFA—Healthcare Financing Administration), has relied on "command and control" types of edicts, McClellan's vision is significantly different. He wants to better utilize market forces to stimulate innovation, improve healthcare quality, control spending, and meet the service expectations of Medicare and Medicaid beneficiaries.

Faced with a tidal wave of new procedures, expensive therapeutic drugs, and diagnostic tests, Medicare is crafting a unique strategic response. "Instead of having 10% to 20% effective success rates over a broad population, we want to get to 80% or 90% who benefit, and with fewer side effects," declared McClellan.

Not Enough Knowledge

One academic expert who praises the new Medicare policy is Robert Califf, Director of the **Clinical Research Institute at Duke University**. "Almost regardless of your political philosophy, this makes sense," he said. "We have an increasingly powerful array of drugs and devices and a bewildering array of choices. And there is broad agreement among people who make these choices that we don't have the information we need."

One trigger behind Medicare's policy is the growing number of cancer drugs which are approved by the FDA for one use, but prescribed by physicians for many off-label uses. When Zevalin (Ibritumomab tiuxetan), manufactured by **Biogen Idec** entered the market, it was approved for non-Hodgkin's lymphoma and cost $25,000 per dose. Medicare officials were concerned that it would be prescribed for off-label uses, without adequate clinical knowledge to confirm the clinical effectiveness of the drug in those applications.

Paying For Off-Label Uses

As a result of this experience, Medicare recently announced that it would pay for off-label uses of four new colorectal cancer drugs for patients enrolled in any of nine clinical trials now getting under way at the **National Cancer Institute** (NCI). These studies are designed to evaluate off-label uses of the drugs.

In another example, on September 15, Medicare announced that it would pay for PET scans performed on people undergoing evaluation for Alzheimer's Disease—but only if the patients are enrolled in a clinical trial that includes a blind "placebo scan" cohort. Manufacturers of PET scanners agreed to fund these clinical trials.

Could Benefit Labs

The potential benefits for the laboratory industry are substantial. Currently Medicare is slow to cover many new diagnostic assays. It places restrictions on when and how the test is covered and often reimburses less than the cost of the basic test kit.

However, this new policy would make it feasible for manufacturers to finance clinical studies even as Medicare reimburses for those new diagnostic tests. During the period of the clinical study, laboratories would be paid for testing. At the end of the study, there would be clinical evidence to indicate whether or not the diagnostic assay has worthwhile clinical benefits. TDR

Medicare's New Policy Involves Substantial $s

HERE IS A SAMPLING of new medical procedures for which Medicare is considering coverage—but only if patients receiving the treatment agree to participate in clinical studies and the clinical studies are funded by reputable third parties.

Treatment/Procedure	Potential Patients/Yr *Cost/Patient
Left Ventrical Assist Device	200 $136,000
PET Scans for Alzheimer's Disease	2-3,000 $1,670
Chemotherapy for Colorectal Cancer	8-10,000 $14,000
PET Scans for Cancer	85,800 $1,670
Implantable Cardioverter-defibrillators	50,000 $35,000

**Estimated*
Source: New York Times

Lab Industry Briefs

KEVIN JOHNSON AND VIJAY AGGARWAL JOIN AUREON BIOSCIENCES

TWO VETERAN LAB EXECUTIVES are back in the business. Kevin Johnson is now the Chairman at **Aureon Biosciences Corporation** and Vijay Aggarwal, Ph.D. is President and CEO.

The fact that both men chose to join Aureon Biosciences will draw attention to the biotech firm. It is developing anatomic pathology capabilities to support personal predictive testing for certain cancers.

Kevin Johnson was most recently President and CEO of **DIANON Systems, Inc.**, prior to and through its sale to **Laboratory Corporation of America** in January 2003. Before that, Johnson held various executive positions at **Quest Diagnostics Incorporated**. Johnson had joined Aureon's Board of Directors in October 2003.

Aggarwal was previously President of **AAI Development Services**, a division of **aaiPharma, Inc.**, a company which develops drugs for the pain management market. Aggarwal had served as President of **Quest Diagnostics Ventures** and had long service at **SmithKline Beecham Clinical Laboratories**.

Aureon Biosciences is located in Yonkers, New York. It was organized by pathologists and scientists from **Memorial Sloan-Kettering Cancer Center** and the **Albert Einstein School of Medicine**. In 2002, it received $15 million in venture capital funding from the **Sprout Group** and **Atlas Venture**.

The company is preparing to bring its first diagnostic product to market. It had a Chairman and President who were venture capital executives. They guided the company in its product development stage. Johnson and Aggarwal will direct the company as it obtains regulatory clearance and begins offering its products to the clinical marketplace.

Aureon is using sophisticated software algorithms to evaluate tissue specimens annotated with the patient's clinical history and outcomes. It simultaneously integrates clinical, microanatomic, and molecular views of the patient to develop a predictive model of the disease. Besides prostate cancer, Aueron is also developing products for breast, lung, and colon cancers.

HOMOCYSTEINE PATENT LAWSUIT SETTLED BY BAYER AND CTI

ANOTHER HOMOCYSTEINE PATENT CASE was resolved on October 26, 2004. **Bayer HealthCare LLC** and **Competitive Technologies, Inc.** (CTI) agreed to settle out of court.

Terms of the agreement grant Bayer a license to use CTI's homocysteine patent. Bayer will pay CTI royalties on sales of Bayer homocysteine assays currently run on its ADVIA Centaur® Immunoassay System and its ACS: 180® SE Automated Chemiluminescence System.

The interesting twist to this agreement is that laboratories who buy homocysteine tests from Bayer will be covered by Bayer's license with CTI. There is also a clause which forgives Bayer's laboratory customers from paying royalties for past tests performed on the Bayer instruments.

CTI notes that the agreement with Bayer does not cover royalties for methylmalonic acid assays done either in the past or the future. CTI will continue to protect its patent on this assay.

In its November 1, 2004 issue, THE DARK REPORT was first to reveal the letter CTI has sent to as many as 700 hospital laboratories and commercial laboratories. This letter demands a licensing payment and back royalties for all homocysteine testing done since January 1998.

Earlier this year, CTI won a federal court case against **Laboratory Corporation of America** for infringement of its homocysteine patent. LabCorp paid the court judgement of $6.7 million. This legal precedent probably played a role in Bayer's decision to settle the case, since LabCorp lost the original case and several appeals.

Although CTI has sent royalty demand letters to hundreds of individual laboratories, its main collection efforts have so far been against the major IVD manufacturers. In public statements on this topic, CTI has specifically mentioned **Abbott Laboratories** and **Axis Shield PLC**.

SOME SOLDIERS INJURED IN IRAQ & AFGHANISTAN HAVE RARE BLOOD DISEASE

MICROBIOLOGISTS will be interested in this under-reported, but developing story. Army doctors report that an unusually high number of soldiers injured in Iraq, Afghanistan, and Kuwait are testing positive for a rare and hard-to-treat blood infection.

The infection involves the *Acinetobacter baumannii* bacteria. At least 102 injured soldiers were diagnosed with the infection between January 2002 and August 31, 2004. These soldiers were primarily at **Walter Reed Army Medical Center** in Washington, DC, **Landstuhl Regional Medical Center** in Germany, and three other military hospitals.

The **U.S. Army** released this information through a report published on November 18, 2004 by the **Centers for Disease Control and Prevention** (CDC). Army doctors are baffled, because it is not known where the soldiers contracted the infections. Prior to Mideast troop deployments following 9/11, military hospitals averaged about one case of this blood infection per year.

"This organism is very widespread in the environment, and some of these patients are arriving with infections," said Maj. Paul Scott, a doctor in the Army's center for health promotion and preventive medicine. *A. baumannii* is found in water and soil. It is resistant to many antibiotics. Colistin, an older drug with high toxicity, is known to be effective against this bacteria.

KAISER READY TO OFFER HEALTH SAVINGS ACCOUNTS TO 25% OF ITS MEMBERS

IT'S A DECISION DRIVEN BY CHANGES in the marketplace. **Kaiser Permanente** will offer its HMO members a new option for 2005 that includes a health savings account (HSA) linked to a high-deductible health insurance policy.

Members in Colorado, Georgia, and the Northwest will have access to this option. These markets represent about 25% of Kaiser's 8.3 million members. The change is driven by growing market demand for lower-cost coverage options. The HSA/high-deductible health plan package is less expensive than traditional health insurance plans for both employers and employees.

One Kaiser executive was particularly candid. "Our customers want to buy it," observed Arthur Southam, M.D., Senior Vice President of Products and Marketing. "This is a very hard change for Kaiser to have that broad discussion about how the evolution of our product portfolio fits into our core values." Among other things, Kaiser Permanente hopes its high-deductible health plan options attract new members. TDR

INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

Community-based pathologists get a featured role on the **Learning Channel's** *Inside Health* program. It will be aired Sunday, November 28 at 8:30 am EST. The Learning Channel used pathologists affiliated with **Pathology Service Associates** (PSA) to help create a segment on the role of pathology in healthcare. PSA plans to make a video of the pathology segment of the program available on its Web site, *www.pathology-billing.com*. The educational program will provide consumers with information about how pathologists help clinicians with diagnosis, prognosis, and monitoring a patient's progress.

US LABS LISTED AS "FASTEST GROWING"

US LABS of Irvine, California is ranked 181 on **Deloitt Technology's** "Fast 500." US Labs, now with annual revenues of $75 million, has posted growth of 1,213% over the past five years. Besides revenue growth, what qualified US Labs for the ranking is its proprietary technology, such as the Virtual Flow™ Only flow cytology tool, as well as its ongoing investments into research and development.

OLD INKJET PRINTERS CAN MAKE HUMAN SKIN FOR BURN PATIENTS

Old **Canon** and **Hewlett-Packard** inkjet printers, with modifications, have been used by researchers to make sheets of human skin which can be used to treat burn patients. The modified printers spray cells onto a gauze scaffolding to create sheets of living tissue. The process starts with the same skin culturing techniques used in skin grafting. "Printing" the cells allows researchers to create a three-dimensional sheet of skin in less time than the current method that uses culturing techniques. Further, the "printed" skin can be engineered to have a protective layer that is more like real skin. This work is being done at **Wake Forest University School of Medicine**, **Clemson University,** and the **University of South Carolina**.

ADD TO: *"Skin Printing"*

It was just 21 months ago, in the February 10, 2003 issue of THE DARK REPORT, that we first disclosed the use of inkjet printers to create complex living tissues. An estimated 9,000 burn patients per year could benefit from an improved source of skin grafts. It is still unknown whether such skin grafts will allow faster healing when used on burn patients, whether the grafts will grow on the body without much scarring, and whether the cells of these grafts might grow uncontrollably, creating a form of malignancy. For these and other reasons, researchers believe clinical applications of the inkjet "skin printing" technology is still several years from becoming a reality.

TRANSITIONS

• Joe Skrisson is the new CEO for **Piedmont Medical Laboratory** (PML) of Winchester, Virginia. This is a laboratory outreach program owned by eight hospitals in the Shenandoah Valley. Skrisson was formerly Director of Business Development at **Beaumont Reference Laboratory** in Royal Oak, Michigan.

That's all the insider intelligence for this report. Look for the next briefing on Monday, December 13, 2004.