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From the Desk of R. Lewis Dark...

THE DARK REPORT

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

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Commentary & Opinion by...

R. Lewis Dark

Founder & Publisher

Investors Returning To Lab Industry

SOMETHING BIG IS HAPPENING to the clinical laboratory industry and the anatomic pathology profession. For the first time in six or seven years, the investment community is paying close attention to the laboratory industry. This should be a welcome development for commercial lab owners and anatomic pathologists.

Behind the scenes and out of the headlines, a number of venture capitalists are looking for business opportunities. These companies want to emulate the success of the private equity investors who funded **Dynacare, Inc.**, **American Medical Laboratories, Inc.**, and **Unilab, Inc.** during the past three years. These companies have also studied the financial performance of **AmeriPath, Inc.**, **DIANON Systems, Inc.**, **IMPATH, Inc.**, and watched the two blood brothers return to financial stability.

Collectively, investors consider this to be evidence that laboratory testing services can generate worthwhile profits. Of course, today's crop of independent commercial laboratory owners knows that making profits is not a guaranteed thing. The same problems of lab overcapacity, declining reimbursement, and decreased test utilization continue to challenge lab owners. Profits remain in a squeeze and the existing generation of lab owners, having survived the 1990s, are somewhat risk averse.

Agree with these assumptions, and you know why it will be outside money and outside management which creates the next generation of laboratory companies. These investors don't care what happened to labs during the last ten years. They concentrate on today's opportunities to make money by providing testing services. They see the passive business strategies of many independent lab companies as leaving the field wide open. They are ready to out-compete existing lab owners.

Overall, I believe renewed interest by professional investors in the clinical laboratory industry will prove to be a healthy development. It will energize the commercial laboratory marketplace while stimulating hospital-based laboratories to become more customer-friendly. Furthermore, it gives owners of today's independent laboratories better opportunities to sell their business, or partner with investors who have the capital and skills to expand their lab's test volumes and revenues. TDR

Merger Creates "New" Pathology Competitor

Two venture capital-backed pathology firms combine and form national path company

CEO SUMMARY: Pathology business consolidation and regionalization continues. Pathology Consultants of America, Inc. (PCA) and PathSOURCE, Inc. announced their intention to merge last month. The combined company will be called Inform DX, Inc. and will compete nationally for anatomic pathology business. Inform DX represents a new business model for the anatomic pathology profession.

TWO WELL-FINANCED anatomic pathology companies joined forces to create a "new" company with ambitions to become a national anatomic pathology powerhouse.

Pathology Consultants of America, Inc. (PCA), based in Nashville, and **PathSOURCE, Inc.** of Port Chester, New York signed a definitive agreement to merge in May.

The merged company is to be renamed **Inform DX, Inc.** and will maintain its corporate headquarters in Nashville, Tennessee.

"Probably the simplest way to describe the motivations behind this merger," said Brian Carr, PCA's CEO, "is that both companies were developing the same capabilities to implement virtually identical business plans.

"In particular, PCA and PathSOURCE were each investing heavily to develop enhanced information capabilities for anatomic pathology," noted Carr. "This merger allows us to combine our efforts and move faster."

"This is a superb marriage because both companies strongly believe that pathology information products are the future of the profession," stated Robert Friedman, M.D., CEO of PathSOURCE.

"Inform DX has a new business model that helps pathologists in academic and general practice settings increase revenue and income by offering 'best medicine' pathology services," he added. "In coming months, we expect to announce several partnering arrangements with respected pathology groups across the country."

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SUBSCRIPTION TO THE DARK REPORT INTELLIGENCE SERVICE, which includes THE DARK REPORT plus timely briefings and private teleconferences, is $10.80 per week in the US, $11.40 per week in Canada, $12.45 per week elsewhere (billed semi-annually).

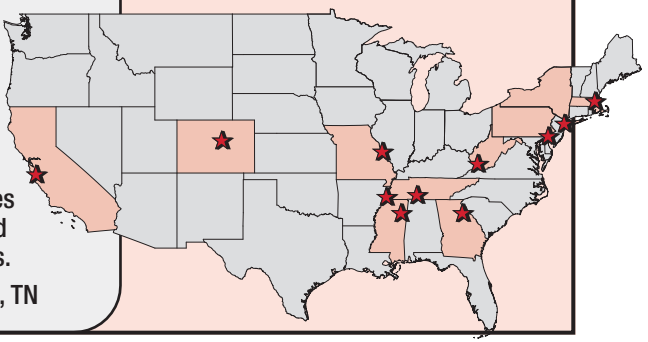
Inform DX *Starts With National Presence*

- Associated Pathology Medical Group
  Los Gatos, CA
- Colorado Pathology Consultants
  Denver, CO
- Columbus Pathology Associates
  Columbus, MS
- Ferrell, Olson, Moore, Pearson, & Bramlett
  Columbia, TN
- Georgia Pathology Consultants
  Gainsville, GA
- Pathology Group of the MidSouth
  Memphis, TN
- PathSOURCE—New England
  Boston, MA
- New England Tufts Univ. School of Med/New England Med Ctr. Department of Pathology
  Boston, MA
- PathSOURCE/Dermpath—New York
  Port Chester, NY
- New York Mt. Sinai School of Med/Department of Pathology
  New York, NY
- PathSOURCE Institute for Dermatopathology—Pennsylvania
  Philadelphia, PA
- Raleigh Pathology Resources
  Beckly, WV
- WCP Pathology
  St. Louis, MO

Inform DX

(After merger between Pathology Consultants of America and PathSOURCE)

- 92 pathologists
- 375 support personnel
- 10 pathology laboratories
- 13 pathology operations in 11 states.
- Estimated annual revenues of $60 million from owned and managed laboratories.
- Headquarters in Nashville, TN



The post-merger Inform DX has two competitive strengths. First is strong financial backing, including improved access to expansion capital. Second is sophisticated management expertise on its board and senior executive team.

Both PCA and PathSource were amply funded by venture capital companies. *(See TDR, February 9, 1998 and November 9, 1998.)* These venture capitalists will continue to participate in the post-merger company.

Post merger, the executive line-up at Inform DX will be as follows: Brian Carr becomes CEO. Robert Friedman, M.D. is Vice Chairman and Richard Jacoby, M.D. is Chief Medical Officer. Haywood Cochrane (formerly CEO of **Allied Medical Laboratories**) will be Chairman. Dan Lufkin, a PathSOURCE investor and one of the founders of **Donaldson, Lufkin and Jenrette**, a major Wall Street brokerage, will be on Inform DX's board of directors.

Inform DX has pathology operations in 11 sites around the United States, involving 92 pathologists. *(See sidebar above.)* Its business plan calls for con-

tinued expansion through acquisitions and affiliations with locally-based pathology groups around the country.

"Our business strategy has five components," noted Carr. "These improve the way pathology services are performed and delivered.

"First, we seek pathology affiliates in key markets," he said. "We want to partner with local pathology groups that have good reputations and can be our anchor for growth in that market.

Pathology Sales Force

"Second, as we move into new local markets, we deploy our sales force to support our local pathologists," continued Carr. "Our financial plan requires double-digit growth in specimen volume and revenue growth. During the past two and one half years, we've successfully accomplished this for our affiliated pathology groups.

"Third, we differentiate our pathologists and our services by offering enhanced pathology information services," he said. "We plan to give referring physicians, patients, and payers a full menu of useful pathology information services.

"Fourth, we want to promote 'best medicine' and 'best information' practices—externally to our customers and internally to our pathologists," stated Carr. "Our growing expertise in pathology subspecialties gives us competitive advantage in local markets and with various HMOs.

"Fifth, we stress 'local pathology' as the main characteristic of our company. Inform DX exists to nurture and support the clinical and financial success of our local pathology partners," explained Carr.

"To achieve this, we have a unique financial model that PathSOURCE developed. It blends the best of the employment business model for investors with the best of the equity business model for pathologists. It basically centers around the acquisition of the laboratory, accompanied by a bonus compensation agreement that provides performance incentives to all partners."

Executives of the new Inform DX believe their recent business experience validates these five strategic business goals. "In the marketplace, we've seen the importance of local pathology services," noted Bill McDowell, Senior Vice President of Development for PCA. "Most pathologists have an excellent market position that gives them a competitive market advantage over national pathology companies.

"For example, local pathologists are known and recognized by area physicians," he explained. "They see inpatient and outpatient specimens that are never sent to national pathology labs. The variety of specimens seen by hospital-based pathologists is also broader than specimens from the physicians' office environment. As part of Inform DX, these local pathology groups can use our sales and marketing skills to build specimen volume and revenues from physician office referrals.

"Inform DX can assemble anatomic pathology information for patients that covers inpatient, outpatient, and outreach testing across several markets," he noted. "It allows our local pathologists to differentiate themselves to managed care plans in their area.

Competitive Advantage

"This competitive advantage at the local level is further enhanced by the subspecialty expertise within Inform DX and our enriched information capabilities," said McDowell.

"Managed care plans recognize and value these attributes. Our pathology groups in Denver and St. Louis have achieved critical mass," he continued. "Managed care companies recognize this. Effectively, we've lever-

aged the work our pathologists do for inpatients to create access to pathology specimens originating in the physicians' offices."

Inform DX recognizes the importance that laboratory data has to the healthcare system. "We believe that sophisticated information capabilities will be a key market differentiator among pathology competitors," said Carr, "and we are already boosting the information capabilities of our existing pathology affiliates."

Information Strategy

"Our information management strategy has three components," noted McDowell. "First, we are moving to web-browser based test ordering and results reporting for all our practices.

"Second, we created a data repository at our Nashville headquarters," he said. "Some practices already feed us, on a daily basis, data on costs, sales/marketing results, QA/QC information and similar items.

"Third, we have a company intranet operational at all sites. It permits us to plug in additional information capabilities as they are developed," commented McDowell.

Inform DX will not standardize information systems across all local practices in the short term. "It doesn't matter whether our practices use AP systems such as CoPath, Cortex, and the like," observed Carr. "We are developing a product that will sit atop their pathology information systems and feed data into our central repository.

Collect Global Data

"We're working with **Stonebridge Technologies** to develop this capability," added Carr. "We expect to roll it out by year's end. It will allow us to generate pathology reports across all sites and collect global data. Stonebridge just finished helping **Esoterix, Inc.** create a similar product. It allows Esoterix's individual labs to feed data into the corporate repository."

The merger of PCA and PathSource into Inform DX creates a formidable new force in the national marketplace for anatomic pathology services. The pathologists and executive team at Inform DX are developing a comprehensive array of pathology services and information products.

Against the trends of healthcare consolidation and clinical integration, Inform DX is investing time and money to help local pathologists move past a single-hospital business focus and position themselves as state-of-the-art pathology providers to physicians, payers and patients.

The market seems to recognize the value of pathology services. Sustained growth in revenues and profits of such national pathology companies as **AmeriPath**, **DIANON Systems**, **IMPATH**, and **UroCor** during the past five years demonstrates that anatomic pathology can be a highly lucrative business.

Outmoded Practice Model

But it won't be lucrative for small, hospital-based pathology practices that refuse to recognize that the 1980's group practice model, based on fee-for-service medicine, is increasingly outmoded in today's healthcare world of integrated hospital networks, managed healthcare, and Internet-based information services.

THE DARK REPORT recommends that pathologists and laboratory administrators explore new ways to package anatomic pathology services. The efforts of companies like Inform DX show how competition is raising the bar and making enhanced pathology services essential for financial success in today's healthcare market. **TDR**

Contact Brian Carr and Bill McDowell at 615-665-4600 and Robert Friedman, M.D. at 914-934-8004.

The Dark Index

1-For-10 Reverse Stock Split Boosts LabCorp's Share Price

MAY PROVED TO BE an auspicious time for **Laboratory Corporation of America** to restructure its equity base. In the process, it's positioning itself to be a tougher competitor in the lab testing marketplace.

Ever since the company was first created by the merger of **Roche Biomedical Laboratories** and **National Health Laboratories** (NHL) in 1995, LabCorp's equity composition of common stock and preferred stock has been a financial handicap. But that situation is now changing.

Restructuring Equity Base

LabCorp launched two initiatives to restructure its equity base. First, after gaining shareholder approval at its annual meeting, LabCorp announced a 1-for-10 reverse split for its common stock. The split was effective on May 3, 2000 and the readjusted price became $63.00 per share. It also reduced the number of common stock shares outstanding to 13.34 million.

LabCorp followed the reverse stock split with a call to redeem its Series A and Series B Convertible Preferred Stock. These shares will convert to common stock at the rate of 1.81818 common shares per preferred share. The redemption will be completed by July 9, 2000.

To convert 100% of the outstanding preferred stock, LabCorp will issue 20.93 million shares of common stock. Once completed, this redemption will increase to 34.27 million the number of common stock shares outstanding.

Laboratory executives and pathologists should remember that, as a publicly-traded company, LabCorp's primary goal is to increase shareholder value. The reverse stock split and the preferred stock redemption programs are designed to make it easier for LabCorp to boost the price of its common stock.

In recent years, a portion of LabCorp's net profits were earmarked to pay dividends on preferred shares. This reduced the money available to pay dividends on common stock, thus depressing the market value of LabCorp's common stock. It was a situation that restricted the company's ability to use its common stock in beneficial ways.

For LabCorp, future sustained increases to the price of its common stock would give it more financial power and make it a tougher competitor in the laboratory marketplace.

Striking Difference

In fact, LabCorp's complicated equity arrangements have been one striking difference between LabCorp and **Quest Diagnostics Incorporated** since Quest's founding on January 1, 1997. Quest Diagnostic's balance sheet and equity structure has been much stronger than LabCorp's in recent years.

This worked to Quest's benefit in a number of ways. For example, because it had the financial strength to absorb the write-down losses associated with closing labs, Quest Diagnostics was able to

restructure several of its marginally-profitable laboratory operations in 1997 and 1998. For Quest Diagnostics, these writedown charges were as much as $60 million in a single year.

LabCorp, on the other hand, did not have the balance sheet capability to absorb such writedowns. As a result, in several markets, it continues to operate a legacy system of laboratories created by Roche and NHL before the merger. An improved balance sheet and equity structure will give LabCorp's executive team more options to address both internal cost-cutting projects as well as external profit-building opportunities.

After LabCorp restructures its common stock and equity base, it must next address its balance sheet. The company needs increased flexibility to raise capital for short term and long term needs, while reducing the amount of money it pays to service its debt. It is reasonable to expect that LabCorp will take significant steps to improve its balance sheet in the coming year. TDR

Two Blood Brothers Continue To Report Increased Revenues

Specimen Volume Jumps at LabCorp

For first quarter 2000, Laboratory Corporation of America saw an 8.1% increase in volume. This is the largest volume increase posted by LabCorp since it was formed in 1995.

More significantly, net sales for first quarter totaled $462.7 million. At this rate, LabCorp will do as much as $1.85 billion in sales for 2000. Earnings before taxes almost doubled from one year earlier, from $22.8 million to $47.6 million. The company was also able to pay down its term loan by $28.9 million during the quarter.

LabCorp's sales growth was paced by an average increase in pricing of 2.6% over quarter one in 1999. Taken collectively, the financial results posted by LabCorp for the first quarter demonstrate the the company's sales and marketing efforts are generating new volumes of business. The higher pricing indicates discipline in resisting payer's attempts to further depress contract pricing for laboratory testing services.

Quest Diagnostics Absorbing SBCL

There was good financial news at Quest Diagnostics Incorporated for first quarter 2000. On a pro forma basis, both specimen volume and average revenues per requisition were up, by 6% and 2%, respectively.

The impact of Quest Diagnostics' acquisition of **SmithKline Beecham Clinical Laboratories** (SBCL) last year is becoming visible. Quest's revenues for the quarter were $857 million, which is an annual run rate of $3.42 billion.

It appears that Quest Diagnostics' efforts to retain SBCL client accounts is succeeding. On a pro forma basis, which assumes that SBCL had been part of Quest Diagnostics for all of 1999, total revenues increased by 4%, along with the healthy 6% increase in the number of patient requisitions.

Other financial measures, such as EBITDA, showed strong improvement. The investment community is responding favorably to these results by bidding Quest's stock to over $60 per share.

Internet Developments

Web-Based Lab Transactions Part of McKesson HBOC's Plan

CLINICAL LABORATORY DATA will play a big role at **iMcKesson**, the new Internet healthcare business unit of McKesson HBOC, Inc., based in San Francisco.

McKesson HBOC is putting existing business assets representing annual sales of $300 million into this new division. They include **Abaton.com**, **Physician Office Manager**, and **Acess Health**, among others.

Real-Time Web Services

iMcKesson intends to offer a full-service menu of real-time, on-line physician office and medical management products and services. Because of McKesson HBOC's existing business relationships with physicians, hospitals, and laboratories, iMcKesson starts with lots of credibility and access.

McKesson HBOC's installed base of software in hospitals and hospital laboratories throughout the United States gives it a unique competitive advantage. It is already in a good position to help many integrated hospital networks develop Web-based access to clinical data and patient records.

iMcKesson's first product offering is an ASP (application service provider) information package that allows physicians to "order lab tests, view results, prescribe medication electronically and maintain patient medical records in the context of existing practice workflow."

This package will also handle administrative needs, such as patient eligibility checks, online claims editing and submission, patient referrals, and claims processing. It also has a patient education component.

It's a major business gamble for McKesson HBOC to convert a huge chunk of its annual revenue base to the ASP business model of thin client and Web browser-based access. McKesson's decision demonstrates how rapidly the healthcare system is converting to Internet-based communication and information management tools.

McKesson HBOC has one important head start over emerging healthcare E-commerce competitors such as **Healtheon/WebMD**. McKesson HBOC already has a sizeable, well-trained sales force in the field. It has 700 people selling to hospitals and health systems, along with another 500 people who call on physician offices to sell medical and surgical supplies.

Striking Difference

Hospital-based laboratories now using McKesson HBOC's LIS products will probably soon see sales reps at their hospital working with administration to implement the iMcKesson business strategy. Things will happen quickly, because McKesson HBOC needs to generate revenue from iMckesson.

THE DARK REPORT predicts that similar reorganizations will be announced by other leading healthcare IS companies. Their goal will be to offer integrated information solutions which, by definition, must include clinical laboratory test ordering and results reporting. TDR

Cost/Benefit Assessment is Complicated

Questions Remain About Performance Of Liquid-Prep Paps

CEO SUMMARY: During the past five years, several companies entered the lab marketplace with claims that their new Pap test technologies are improvements over conventional Pap smear methods. Armed with investment capital from Wall Street, these companies launched aggressive sales and marketing campaigns to clinical labs, pathologists, payers, physicians, and women. The diversity of advertising claims has, at a minimum, caused much confusion among laboratorians about the true cost/benefit effectiveness of various new Pap test technologies. Our guest writer attempts to sort through the various issues.

PART ONE OF A SERIES

BY JOSEPH PLANDOWSKI

EDITOR'S NOTE: Despite FDA approval of several competing new technologies for Pap testing, there continues to be a lack of consensus within the pathology profession and the clinical laboratory community about the benefits and cost-effectiveness of these products.

Joseph Plandowski tracks and studies new Pap test technology. He was a director for an emerging cytology products company that offered an enhanced cytology microscopy work station system to cytology laboratories. In this first of a multi-part series on the market acceptance of new Pap smear technologies, Mr. Plandowski presents seldom-publicized aspects of the way data from studies is used to support the aggressive marketing of these new Pap test technologies. In future installments, he will look at the economic impact to labs when they switch from conventional Pap smear methods to these new Pap test technologies.

IN THE BATTLE TO INTRODUCE new technology to conventional Pap smear testing procedures, there is no shortage of sales and marketing efforts.

In particular, marketing campaigns to introduce liquid-based preparation (LBP) products have been intense. These include innumerable trade shows, journal advertising, television commercials, press releases, brochures, and self-interest groups hyping liquid-based preparation kits for Pap testing.

Two companies currently have FDA clearance to market LBP Pap tests. **Cytyc Corporation** received clearance for its ThinPrep® product in May 1996. Almost three years later, in June 1999, **TriPath Imaging, Inc.** (formerly **AutoCyte, Inc.**), received clearance for its PREP® product. These products are also known as thin-layer preparations (TLP).

In the race to build market share for LBP Pap test kits, Cytyc currently enjoys a huge market share lead over TriPath. I believe this is due primarily to Cytyc's marketing prowess, rather than its earlier clearance by the FDA. Interestingly, Cytyc and TriPath are embroiled in several lawsuits against each other, including a Cytyc-initiated lawsuit claiming cryopreservative patent infringement by TriPath. If it can't be defended, the result may have a severe adverse effect on Cytyc. Don't be surprised if this becomes a tortoise-and-hare scenario.

Background To Pap Issues

After several years of marketing efforts to women, physicians, and laboratory management, there is plenty of confusion about the true costs and clinical benefits of new Pap test technologies. That's because these companies selectively emphasize the most positive aspects of trials and studies involving their products. This means that other clinical data from the same study which may indicate questionable, even negative results, are not brought to the attention of potential customers, users, and laboratory managers.

Thus, it is not without justification that a number of very knowledgeable and experienced cytopathologists have complained that the full and true story about the clinical efficacy of new Pap smear testing technologies has yet to be brought into public debate. They point out that women, physicians, laboratory managers, payers, and even Wall Street investors are only getting selected parts of the story from the collective group of emerging cytology companies.

It's an undisputed fact that conventional Pap smear methodology is complex. It requires a fairly sophisticated understanding of this process to best understand why Pap smear testing is an effective screening method for cervical cancer.

This sophisticated understanding certainly does not exist among women in the lay public. And even physicians who regu-

Bethesda System Terms Complex for Lay Women

There are infinite variables which affect the results of any laboratory's particular Pap smear screening program.

That is why current methods used in Pap smear screening represent a complex process. Comparing the results of independent clinical studies across a number of screening sites is challenging even to the experts.

The Bethesda system of Pap smear classification is in wide use. For lay women, understanding the ramifications of its most common categories can be problematical.

- **ASCUS (atypical squamous cell of undetermined significance):** These cellular changes exceed those which can be a benign process, but fall short of an intraepithelial lesion or cancer. Many of these will revert to normal. 10% to 15% will progress.
- **LSIL (low-grade squamous intraepithelial lesion):** This is the HPV category. Low-grade SIL (HPV/mild dysplasia/CIN1). About 25% will have a high grade SIL at colposcopy. Lesion has a 15% chance of progression to in situ cancer (CIS).
- **LGSIL (high grade squamous intraepithelial lesion):** High-grade SIL (moderate and severe dysplasia/CIN 2, 3, and CIS). Lesion has a 50% chance of progression to CIS.
- **Squamous cell carcinoma:** probable invasive cancer, requires histology.

(Classifications taken from University of Kansas Medical School training materials,© 1998)

larly offer their patients Pap smear tests, may lack the up-to-date clinical sophistication to correctly evaluate the results from a particular study of a specific new Pap smear technology.

It is the complexity of the conventional Pap smear testing process, then, that makes it easier for emerging cytology technology companies to advertise and position their products in ways that can generate misperceptions among physicians, payers and patients.

For example, Cytyc promotes its thin-layer preparation Pap smear test as a "replacement" of the conventional Pap test. As a result, journalists and commentators, untrained in clinical cytology, prepare newspaper and television features which refer to the LBP Pap test as a technological breakthrough that has replaced an old technique, the conventional Pap smear.

LBP is Not A Replacement

In reality, LBP is an *additive step* in the conventional Pap smear process, not a replacement of the process. Moreover, thin-layer preparation itself is not a new technology. For almost 20 years, thin-layer preparation has been used for many types of specimens. The "newness" is in its application to Pap testing.

To put the LBP Pap test into perspective, it is important to briefly review conventional Pap smear methodology. That process begins in a physician's office where cervical cells are collected with a cell collection device and smeared onto a microscope slide. The physician immediately sprays the cells with a fixative to prevent air-drying of the cells, then sends the slide to the lab.

When the laboratory receives the Pap smear slide, it stains the cells and protects them by adding a plastic or glass coverslip over them. The slide is now ready for screening by a cytotechnologist. All slides containing abnormal cells are referred to a pathologist for final diagnosis.

When thin-layer Pap products are used, the process follows a similar procedure. A physician still collects the cervical cells. But instead of smearing the

cells onto a microscope slide, the physician inserts the cell collection device with collected cells into a vial containing a proprietary solution that preserves the cells until they reach the laboratory.

At the laboratory, the vials are processed in proprietary devices (instruments) which separate the cells from the preservative solution. Then the cells are deposited in a 13 mm diameter (TriPath) or a 20 mm diameter (Cytyc) thin-layer circle on a microscope slide. The cells are stained and protected by a glass or plastic coverslip. Now the slides are ready for screening by a cytotechnologist. If an abnormality is found, the slide is reviewed by a pathologist.

It's important to recognize that, once a slide is prepared by either the conventional or thin-layer method, the remainder of the Pap smear process is virtually identical. The sole difference is that, in the LBP Pap test, collected cells are put directly into a proprietary preservative solution rather than cells being smeared onto a microscope slide (as in the conventional manner).

LPB Is Not A Replacement

Thus, when representations are made that the LBP Pap test is a replacement to conventional Pap testing, it should be noted that only the step between cell collection and deposition onto a microscope slide is different. Otherwise, the entire process is the same in either case. That is why LBP *does not* replace the conventional Pap test process.

Probably the most controversial part of the debate about the clinical efficacy of liquid-based Pap preparations centers around "sensitivity" (the ability of a diagnostic test to accurately identify a positive specimen), and "specificity" (the ability to not identify a negative specimen as being positive). It is acknowledged that conventional Pap smear screening methodology has relatively low rates of sensitivity and specificity. Yet, with regular screening cycles, this is sufficient to make conventional Pap smears a highly-effective diagnostic screening test.

Thus, it is against this background that the claims of various new Pap technology companies must be evaluated. After reviewing the clinical data supplied by Cytyc's ThinPrep and TriPath's PREP, the FDA issued clearances that allow both companies to at least claim equivalence with conventional Pap smears.

Additional FDA Clearance

But Cytyc also received an additional clearance from the FDA in November 1996. This permitted it to expand its claims for ThinPrep to include improved effectiveness in detecting LSIL and more severe lesions versus a conventional Pap smear (improved sensitivity), based on results from a subset of its clinical trials sites dubbed "screening centers."

In contrast to labs serving a high risk population, these Pap smear screening centers had a relatively low prevalence of disease, thus increasing the likelihood of false positive diagnosis. As most pathologists know, many screening tests will show higher sensitivity if the specificity is lower, i.e., a higher number of false positives are generated. In this particular clinical study, when Mark Sherman, M.D. adjudicated the slides, he confirmed a large number of false positives from these three screening centers.

The most recent papers published during 1999 corroborate Cytyc's claims for increased sensitivity. However, other results in those papers present disturbing findings that are not noted in any of Cytyc's press releases.

One of the papers, authored by Martha L. Hutchinson, M.D., appeared in the April 25, 1999 issue of *Cancer (Cancer Cytopathology)*, a prestigious

and well-respected journal. This is a particularly good study to review, because histology ws done on the non-negative Pap results. In the paper, Dr. Hutchinson reports that compared to the final diagnosis, ThinPrep detected 93% of the cases with HSIL and 100% of the cases with carcinoma. This compares with the conventional Pap smear which detected 78% and 91%, respectively.

Other Important Finding

Cytyc issued a press release on April 28, 1999 which trumpets these results. However, entirely absent in Cytyc's press release is Dr. Hutchinson's other important finding. That is, improvement in detection rates came with "a concurrent significant increase in colposcopy referrals."

Specifically, 1,095 of the 8,636 patients (13%), screened by ThinPrep underwent a colposcopy. Of the 1,095 patients, only 565 (52%) were judged to have an actual abnormal Pap test after colposcopy.

In contrast, conventional Pap smears done on these same women resulted in 579 (7%) receiving a colposcopy. Of the 579 patients, 451 (78%) were judged to have an abnormal Pap test. Colposcopy with biopsy is an uncomfortable, if not painful procedure. It is also expensive. In any event, the supposed increase in disease detection by the ThinPrep product can be attributed to overdiagnosis (false positives).

Final Diagnosis

Another finding that Cytyc did not mention in its April 28, 1999 press release is that the ThinPrep diagnoses agreed with final case diagnoses in 7,379 of the 8,636 patients (85%) compared to 7,669 of the 8,636 patients (89%) who had a conventional Pap smear.

The conventional Pap smear concurred with the *final diagnoses* in 290 more cases than ThinPrep! In my opinion, this particular clinical result certainly does not support an argument that Cytyc's thin-layer preparation is an improvement over conventional Pap smear preparation methods.

Dr. Hutchinson's study was supported by the **U.S. National Cancer Institute**. Her paper is interesting reading even for the layman. For example, ThinPrep's 93% HSIL detection rate was determined from its ability to detect 117 of the 126 cases with HGIL as a final diagnosis.

And, ThinPrep's 100% carcinoma detection rate was determined from its ability to detect all 11 of the cases with a final diagnosis of carcinoma. This compares with the conventional Pap smear, which detected 98 of the 126 HGIL cases and 10 of the 11 carcinoma cases. All of these cases are from a population study of 8,636 patients.

Issue Of Overcall

But both of these results do not reflect the issue of overcall—of sensitivity versus specificity. If the cytotechs in this study were to define every slide as abnormal, sensitivity would be 100% (because no actual abnormals were missed), but the specificity would be zero (because every normal slide was judged to be abnormal).

Dr. Hutchinson summarizes her paper "suggesting that the ThinPrep method is *at least as good as conventional cytology* [my italics] in detecting SIL and carcinoma." Dr. Hutchinson is at **Women & Infants Hospital**, **Brown University**, Providence, Rhode Island.

Two pathologists from the **Quest Diagnostics Incorporated** laboratory in Boston did a study of ThinPrep and published their findings in the September 1999 issue of *Archives of Pathology and Laboratory Medicine*. Cytyc quickly issued a press release on September 15, 1999. It heralded ThinPrep's 103% increase in the detection of HSIL and a 73% increase

Issues of Sensitivity and Specificity Greatly Influence Outcomes of Studies

Why is there so much disagreement and debate about the interpretation of studies involving liquid-based preparation (LBP) systems for Pap test screening?

It is because the analysis and interpretation of sensitivity and specificity for diagnostic screening tests is like a Gordian Knot—convoluted, complex, and unclear.

To calculate sensitivity, one must know how much true disease actually exists in the test population—this is the denominator. In most studies of LBP Pap test technologies, the denominator is unknown. Thus, physicians conducting studies do not calculate "sensitivity" as such, but rather "improved detection." Moreover, they typically do not prove that the additional disease detection is real (actual positive) versus false positives.

That is because, if the denominator (true disease in a studied population) is unknown and the study does not exclude false positives, any answer is possible and all answers are probably wrong.

$$\text{Sensitivity} = \frac{\text{detected disease}}{\text{total true disease}} = \text{1-false negative fraction}$$

$$\text{Specificity} = \frac{\text{detected normal}}{\text{total true normal}} = \text{1-false positive fraction}$$

in the detection of LSIL compared to the conventional Pap test.

Omitted in Cytyc's press release is any mention of a 26% decrease in detection of carcinoma reported in this study. The press release also failed to disclose that, in this study, ThinPrep generated a 205% increase in the number of cases diagnosed as "unsatisfactory for evaluation."

In this same study, the authors also presented data for a subset of physician accounts that completely switched their patients to the use of ThinPrep. Here the increase in detection is even more dramatic. It rises to 129% for HSIL and 74% for LSIL. However, all cervical cancers in this subset of patients were missed, not an insignificant finding. Furthermore, the percent of cases diagnosed as "unsatisfactory for evaluation" increased to 300%.

Pathologists and laboratorians will recognize the problems caused by a diagnosis of "unsatisfactory for evaluation." Standard practice for any patient with a Pap test diagnosis of "unsatisfactory for evaluation" is to repeat the test. Both the physician and the laboratory generally perform this follow-up Pap test at no cost to the patient.

Thus, any new Pap test technology which generates an increased number of "unsatisfactory for evaluation" diagnoses triggers a cascade of additional (and unreimbursed) costs to the physician and the laboratory. In addition, the patient is inconvenienced and often irate at her physician.

"Unsatisfactory" Paps

Finally, as laboratories well know, a higher rate of "unsatisfactory" Pap test diagnoses frequently causes the referring physician to switch the account to a competing laboratory. Since OB/GYN accounts are among the most profitable of physician specialties for laboratories, loss of this business is financially painful.

In recent years, several marketing and advertising campaigns by the various vendors of new Pap test technologies created problems for OB/GYNs. Many women, after reading advertise-

ments and media stories on why new Pap test technology is "better," began to doubt the effectiveness of the conventional Pap smear. Physicians were asked by these women why their office didn't offer these "new" and "better" Pap tests.

Dealing with concerned, fearful female patients proved to be a significant problem. That is why the **American College of Obstetricians and Gynecologists** (ACOG) declared its position on recently-introduced Pap test technologies. In a news release dated July 31, 1998, ACOG stated "Despite the recent FDA approvals of new Pap test screening techniques (ThinPrep, AutoPap®, PAPNET®), these technologies do not represent the current standard of care in cervical cancer screening."

ACOG went further to explain that it "issued the document partly in response to aggressive direct-to-consumer advertising that led many women to feel they are at greater risk for undiagnosed cervical cancer if they don't use the latest technology."

Exactly one year later, July 31, 1999, ACOG issued another news release stating "Invest health resources in widespread Pap screening, not new technologies." ACOG argues that "new cervical cancer screening technologies are not likely to help women most in need of cervical cancer testing and could even widen the economic gap between women who get Pap smears and those who don't."

Compared Technologies

The **U.S. Department of Health and Human Services** (HHS) issued a lengthy and detailed report in April 1999 entitled *Evaluation of Cervical Cytology*. HHS compared the new technologies for cervical cytological screening with conventional Pap testing in terms of diagnostic accuracy, costs, effectiveness, and cost-effectiveness in adult women. HHS findings were revealing. It stated that "the imprecision in estimates of effectiveness and the cost of the new [Pap test] technologies makes drawing firm conclusions about their relative cost-effectiveness problematic."

Clearly, the specific studies cited here show that the clinical effectiveness of thin-layer based preparation for Pap testing has yet to demonstrate clear superiority over conventional Pap smear preparation. In fact, there is credible evidence that LBP Pap smears actually add costs to the healthcare system without contributing clinically and economically worthwhile benefits.

Additional Clinical Studies

Additional studies now under way may help resolve these issues. In the meantime, there are several other areas of concern that involve LBP Pap tests. Some of these are:

1) A study published in *The American Journal of Clinical Pathology* in February 1994 reported that, with conventional Pap smear collection and preparation, as much as 80% of the collected cells are not transferred to the slide, but discarded with the collection device. The discarded cell collection device may contain abnormal cells. However, most conventional Pap test slides contain an average of 150,000 to 300,000 cells.

While the LBP collection process saves all the collected cells in the preservative fluid, only about 50,000 cells are deposited on the slide. The rest remain in the preservative fluid. If there were 300 abnormal cells on the cell collection device containing 500,000 cells, LBP technology does not ensure that all those 300 abnormal cells would be deposited on the slide. Statistically, only 50 abnormal cells would be put on the slide. The other 450 abnormal cells remain in the preservative fluid which is eventually discarded. With a low prevalence of abnormal cells, there is also the possibility that none of them end up on a slide prepared by thin-layer methods.

2) When Cytyc supplied data to the FDA under its original application, the data from ThinPrep's six clinical trial sites left some unanswered questions. The six sites were equally split between hospital laboratories and screening centers, and encompassed 6,747 patients.

The results were far from equal. The hospital laboratories demonstrated only a 6% improvement in disease detection using ThinPrep versus conventional Pap tests while the screening centers demonstrated a 65% improvement. When averaged, the overall results demonstrated an 18% improvement. But this 18% improvement does not include the FDA-required adjudication of results from the different sites to determine the actual diagnostic truth. In fact, that adjudication, when done by Mark Sherman, M.D., showed only a 5% increase in sensitivity, which was not statistically significant.

This site disparity was of concern to some in the industry and resulted in letters to the FDA questioning its clearance of ThinPrep. TriPath's submission of data to the FDA was supported by studies on 8,983 patients from eight sites. Its PREP liquid-based Pap test demonstrated an improvement of 17% in screening sensitivity relative to the conventional PAP smear.

Observation & Conclusions

I find it surprising that, after several years of working with these new Pap test technologies, two things have failed to occur.

First, despite an ever-increasing volume of day-to-day clinical experience with these new Pap test technologies, no clear consensus exists among pathologists and laboratory executives about whether these products really do make a positive contribution.

That, in itself, may be an important observation. Healthcare technology that is robust and effective usually gains widespread acceptance with a minimum of opposition and criticism. Certainly the current ongoing debate by laboratorians about new LBP Pap test technologies indicates that the products themselves have failed to demonstrate a clearcut superiority that would engender unanimous support.

No Compelling Argument

Second, no manufacturer of the several new LBP Pap test technologies seems to have funded a sizeable and comprehensive clinical study that, by its size and design, would make a compelling argument that its technology is unquestionably more cost-effective than conventional Pap smear methodology.

Pap smears contribute to women's health, and that is a politically-correct goal which attracts an abundance of grant money from foundations, charitable trusts, and the government. It would certainly seem reasonable that these entities would fund a sizeable study for any new Pap test technology that would improve women's health and add value to the healthcare system.

For laboratory managers and pathologists currently evaluating new LBP Pap test technologies, I would suggest that the lack of lab industry consensus, combined with the lack of any compelling, irrefutable cost-effectiveness, means that most new LBP Pap test technologies may not yet be "ready for prime time."

Rather, these new products may have great application in specific laboratory organizations which serve unique populations around the United States. But for most labs, there remain more questions than answers about the true cost/benefit performance of various new Pap test technologies. TDR

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COMING: A look at the efficacy of automated Pap smear screening systems and how clinical laboratories should calculate the true costs of acquiring and using new Pap smear technologies.

Lab Industry Briefs

FORMER SBCL PRESIDENT HAS QUICK TOUR AS CEO OF PROXYMED, INC.

IT WAS A SHORT TOUR OF DUTY as Chief Executive Officer at **ProxyMed, Inc.** for John B. Okkerse, Jr., Ph.D.

On May 19, after only six months as ProxyMed's CEO, Dr. Okkerse stepped down as part of a cost-cutting move at the financially-beleagured company. Along with Okkerse, ProxyMed's Chief Financial Officer, Chief Operating Officer, Chief Marketing Officer and a senior sales executive also vacated their positions.

Okkerse, formerly the President of **SmithKline Beecham Clinical Laboratories** (SBCL), had assumed CEO duties at ProxyMed in November 1999. It was a logical tie-in for Okkerse and ProxyMed, since the company offers connectivity products to physician offices which include laboratory data.

In fact, in December, ProxyMed signed a contract with **Laboratory Corporation America** to allow physicians to order tests from LabCorp using ProxyMed's ProxyNet® physicians' Web portal.

ProxyMed's 1999 sales were $29.0 million, but losses from acquisitions and continuing operations have put the company in a crisis mode. There is no word on Dr. Okkerse's career plans since his departure from ProxyMed.

INTERNET SECURITY FOR PHYSICIAN TRANSACTIONS IS APPROACHING

Here's a development of high interest for laboratory executives and pathologists offering Internet-based services. **MedePass, Inc.** of California is preparing to offer "digital certificates" to physicians and other healthcare providers.

These certificates are "computer files that act as electronic identification cards, or signatures [and] allow participants at both ends of an Internet communication to know with certainty that the other user is, in fact, who he or she claims to be."

The **California Medical Association** will participate in the credentialing process that creates the certificate. The Social Security administration and several healthcare companies, including **Kaiser Permanente**, have already agreed to accept these certificates.

ROUGH WATERS AHEAD FOR MEDICARE HMOS

EXPERT OBSERVERS PREDICT that many managed care companies are about to pull out of the Medicare HMO program.

These predictions were triggered by **Cigna Corporation's** announcement, on June 4, that it would cease to offer Medicare HMO programs in a number of urban markets. Approximately 104,000 Medicare beneficiaries will be affected.

In some markets, **Aetna, Inc.** has stopped advertising and accepting new members to its Medicare HMO. By July 1, Aetna may follow Cigna in exiting the Medicare HMO business.

Currently there are about 6.2 million seniors enrolled in Medicare HMO plans throughout the country. This is about 16% of Medicare-eligible individuals.

This development may help clinical labs now providing testing services to Medicare HMOs. Since lab contracts are capitated, migrating Medicare HMO beneficiaries back to fee-for-service care will boost lab test revenues generated by these patients. TDR

INTELLIGENCE LATE & LATENT

Items too late to print, too early to report

At **DIANON Systems, Inc.**, recent growth in revenues and profits may cost the anatomic pathology company its independence. In recent weeks there's been widespread speculation that DIANON may be involved in some type of acquisition or merger negotiations. At various times, each of the two blood brothers has been rumored as an interested party. As of press time, there has been no official comment on this matter.

ADD TO: DIANON SYSTEMS

With the sustained financial performance of anatomic pathology companies such as **AmeriPath**, DIANON, **IMPATH**, and **UroCor** during the last half of the 1990's, Wall Street investors are getting excited about the financial opportunities in anatomic pathology. But it seems that the last people to pay attention to this opportunity are pathologists themselves. Pathologists, not outsiders, should take the lead to create and control the next generation of anatomic pathology companies and group practices.

HOSPITAL GPOS WANT STANDARDIZED BUYING PRACTICES

Once again, the threat of the Internet is bringing healthcare competitors to the same table. This time it's three of the hospital group purchasing organizations (GPO): **Consorta**, **Novation**, and **Premier**. They've signed agreements with e-commerce vendors **Medibuy.com**, **EmpactHealth.com**, and **Neoforma.com** to create a committee, called "the e-standards work group." This committee will work to get manufacturers and distributors to develop common standard product codes that would uniquely identify medical supplies, including laboratory reagents, instruments, and similar products.

MORE ON: BUYING CO-OP

This initiative indicates that GPOs expect electronic purchasing exchanges to develop into viable tools. It shows how Internet e-commerce will transform the current way medical products are purchased. For hospital laboratories, the emergence of electronic purchasing exchanges is expected to provide new opportunities for labs to squeeze out costs through improved purchasing techniques. Also, the absence of standard nomenclature for even the most simple items, such as bandages, has enabled manufacturers and distributors to extract a higher price from hospitals and laboratories, due to the difficulty of cross-comparing similar products.

NEW PRESIDENT AT TRIPATH IMAGING

TriPath Imaging, Inc. of Burlington, North Carolina , maker of the PREP® and AutoPap® systems, announced that Paul Sohmer, M.D. would be its new President and Chief Executive Officer (CEO). James B. Powell, M.D. will relinquish his presidential duties to Sohmer and move to Chairman. Sohmer was most recently the President and CEO of **Neuromedical Systems, Inc.**, and has held executive positions at **Nichols Institute**, **Genetrix**, and several other lab companies.

That's all the insider intelligence for this report. Look for the next briefing on Monday, July 10, 2000.

THE DARK REPORT

UPCOMING...

- *Part Two: How Labs Can Calculate the True Cost of Using Enhanced Pap Smear Technology.*
- *Solving the Laboratory and Pathology Billing and Collections Dilemma: Ten "Must Do" Management Priorities.*
- *Hospital-Based Laboratories Regaining Local Market Dominance By Using Unique Management Strategies.*
- *The Best Management Training Program For Today's Emerging Lab Leaders.*