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Valerie Palmieri, Momentum Consulting on…

How to Protect Your Lab's Proprietary LDTs and Assess the Financial Impact of Compliance

Essential actions labs should take now

(See pages 15-16)

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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

Unpacking the Surprises in the FDA LDT Rule

THERE ARE NOW TWO LAWSUITS IN TWO DIFFERENT FEDERAL COURTS CHALLENGING THE **FOOD AND DRUG ADMINISTRATION'S** AUTHORITY to regulate laboratory developed tests (LDTs). The first was filed on May 29, 2024, by the **American Clinical Laboratory Association** (ACLA). The second was filed on Aug. 19, 2024 by the **Association for Molecular Pathology** (AMP).

However these lawsuits play out, there is a consensus among many lab professionals who have studied the rule and know something about the sentiment in **Congress** towards the issue of how LDTs might be regulated that some form of regulation of LDTs is inevitable. In their reading of the tea leaves, several attorneys contacted by THE DARK REPORT observed that a current version of the Verifying Accurate Leading-edge IVCT Development (VALID) Act is still pending in Congress. They noted there is an opportunity for this pending bill to be reshaped and passed in some form. But that is not a sure bet.

Against this background, there is recognition among many laboratory organizations that—as currently written into law—there are time-consuming and essential steps that must be taken to bring their respective LDTs into compliance with the FDA's final rule that took effect on May 6, 2024.

To help clinical laboratories, genetic testing companies, and anatomic pathology practices understand how best to comply with this rule, THE DARK REPORT is presenting a comprehensive webinar on Sept. 12, 2024. The three presenters will provide you with a detailed understanding of what is required by the FDA's LDT Rule; how to assess your lab's menu of LDTs to identify which LDTs have the greatest value in patient care and revenue; and the practical steps to ensure timely compliance, including steps to implement the FDA's quality control standards by next summer's deadline.

There are many hospital and health system laboratories which have dozens of LDTs in multiple departments. Given the importance of these LDTs in the patient care provided by these hospitals and health systems, it is imperative that lab leaders know what the LDT rule requires and have staff and systems in place to comply with the rule.

Yes, there is the possibility that a federal judge may overturn the LDT rule or delay its implementation, but as noted above, there are tea leaves that indicate some form of federal LDT regulation and oversight is inevitable. TDR

Uncertainty in Market for Digital Path Products

Assuming a consensus that pathology's future is digital, why are path groups slow to adopt?

CEO SUMMARY: These are uncertain times for many companies offering a range of digital pathology (DP) products to the nation's pathologists. Sales lag behind projections that caused investors to pour money into numerous DP start-ups. One reason DP companies are not meeting sales goals is the inherent caution common with pathologists when it is time to make substantial capital investments in their labs. This multi-part intelligence briefing looks at factors at play in the DP marketplace.

INTRODUCTION

TODAY, THE CONVENTIONAL WISDOM OF THOSE INVOLVED is that the future of anatomic pathology will be fully digital. There is consensus that nearly all pathologists in the future will work only with whole slide images (WSIs), supported by a digital workflow.

Despite this general consensus of digital pathology (DP) as the future state of anatomic pathology, the most enthusiastic supporters of DP continue to be disappointed at its slow rate of adoption here in the United States.

This special intelligence briefing—presented in three parts—identifies the factors retarding a faster adoption of digital pathology. Before going further, however, it is necessary to call attention to the elephant in the room.

That elephant is the lack of reimbursement for digital pathology services. Pathology laboratories today cannot be reimbursed for the costs of using digital pathology to improve patient care. This means pathology labs are on their own to finance their acquisition and deployment of full digital pathology systems. Until payers establish appropriate reimbursement for diagnostic services incorporating digital pathology tools, adoption will remain slow.

Meanwhile, there is enthusiasm for use of DP in patient care. Each year, attendance at the **Digital Pathology Association's** (DPA) Pathology Visions conference is robust. Pathologists currently using DP solutions in their regular work processes document improvements in workflow, gains in pathologist produc-

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R. Lewis Dark, Founder & Publisher. Robert L. Michel, Editor.

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tivity, certain cost reductions because of digital workflow, and faster answers to referring physicians and their patients.

The well-attended exhibition has companies showing what's available now and what's coming soon with scanners, artificial intelligence (AI) solutions, image analysis algorithms, and more.

However, each year, the vendors selling digital pathology products and services struggle to convince pathology group practices and pathology lab companies that now is the time to "go fully digital" and purchase scanners, monitors, and pathologist workflow solutions.

➤Today's Reality for DP

This intelligence briefing looks at the dichotomy between the expectation of a fully DP future and today's reality of lackluster demand for DP products and services. It is organized in three parts.

Part One: Why so many mid-sized and smaller pathology group practices and pathology labs continue to defer investing in scanners and a digital pathology workflow solution for pathologists. THE DARK REPORT identifies some of the common attributes of these lab organizations responsible for their reluctance to invest heavily in DP in recent years.

Part Two: What happened to the five most prominent companies that entered the U.S. marketing with digital pathology systems between 2000 and 2020. This retrospective confirms one likely reason why pathology groups have been wary about investing substantial capital to buy and deploy a comprehensive DP system.

Part Three: Recent developments involving what THE DARK REPORT calls "the DP class of 2021." This class is made up of four nascent digital pathology companies organized with the primary stated goals of developing and selling digital image analysis algorithms powered by AI. Collectively, these four companies raised $326 million from investors in the first half of 2021.

The DP Class of 2021 can be seen as bellwethers for the current state of the digital pathology market in the U.S.

The first wave of labs adopting digital pathology happened during the 2000s. This wave consisted primarily of the pathology departments of academic medical centers and medical schools. DP technology such as scanners and monitors were typically acquired for three functions:

- To create whole slide images (WSIs) to use in teaching residents and fellows.
- To have digital images for display during tumor board meetings and cancer conferences within the institution.
- To expedite second opinions without the need to courier glass slides to different locations.

The second wave of DP adoption started after 2010 and continues to the present. This is when national pathology companies and the larger pathology regional supergroups began to acquire full digital pathology systems.

Additionally, academic center pathology departments began to build out their use of digital pathology. They increased storage to archive the digital images. They acquired more scanners and monitors and recognized the need to purchase a full pathologist workflow solution to boost productivity, save money, and interface with existing pathology laboratory information systems (LIS).

➤Boost Case Referrals

During this time, some specialist pathologists recognized the opportunity to use digital pathology to boost their national and international case referrals. This practice continues today and is creating a new model for specialty pathology.

Hints of a third wave of digital pathology adoption became recognizable. Mid-sized and smaller pathology groups now acknowledged that DP was becoming an essential tool for being fully competitive.

Who Are the Current Digital Pathology Players? A Scorecard Helps Identify Each Firm's Niche

EACH YEAR, NEW COMPANIES EMERGE THAT WANT TO SELL THEIR DIGITAL PATHOLOGY PRODUCTS AND SERVICES FOR USE IN CLINICAL SERVICES. Often, these companies have an established presence with customers in the pharmaceutical and biosciences. They started in these sectors because—before they could sell these same products to anatomic pathology laboratories for use in patient care—they would have to incur the time and expense to have the federal **Food and Drug Administration** (FDA) review and clear for market these same products.

One good place to learn which companies have digital pathology solutions is the vendor directory on the website of the **Digital Pathology Association**. A recent check showed these vendor categories and the number of companies listed in each category:

- Hardware: 27 companies
- Software: 43 companies
- AI: 29 companies
- Services: 33 companies
- IT: 14 companies
- Biopharma: 8 companies

Note: Some companies were listed in multiple categories.

Different Mix of Offerings at DP Companies

Last year, at a digital pathology workshop, an investment banker showed an internal document to illustrate the cross-functional product strategies of a handful of the companies operating in the digital pathology (DP) sector. The objective was to illustrate that most companies are concentrating their product offerings in one or two DP functional areas, as follows (listed alphabetically):

Integration & Implementation

- Epredia
- Gestalt
- Hamamatsu
- Leica BioSystems
- Motic
- Philips

Artificial Intelligence

- Deep Bio
- Gestalt
- IBEX Analytics
- Mindpeak
- Paige
- PathAI
- Proscia
- Visiopharm

Workflow Solutions

- Gestalt
- Inspirata
- Paige
- PathPresenter
- Proscia
- Sectra
- Smart in Media

The point of this table is to illustrate that today's marketplace for digital pathology products and services requires most pathology groups and pathology laboratories to engage more than one DP company to achieve a full transition to totally digital pathology services. One interesting observation is that the only company listed in all three functional categories is Gestalt Diagnostics. This must be a market-winning business strategy for Gestalt Diagnostics, as it is the only digital pathology company on the list above to grow rapidly enough to have made *Inc. Magazine's* 2023 "5000 Fastest Growing Private Companies in America." Gestalt was 3835 on the list.

Another factor that distinguishes the third wave is the arrival and use of image analysis solutions powered by artificial intelligence, deep learning, neural networks, and similar technologies. The third wave is nascent at this stage, as the market seems to want more FDA reviewed and cleared digital image analysis solutions.

The special intelligence briefings that follow will give pathologists and their practice administrators a fuller appreciation of the market forces at play in the adoption of digital pathology systems. Here is a starter list of these factors, as presented in the parts 1, 2, and 3 that follow:

- No defined reimbursement for digital pathology diagnostics services. Pathology labs incur additional costs without offsetting reimbursement.
- Substantial capital cost to acquire and deploy a complete digital pathology system, including scanners, monitors, pathologist workflow solution, interface to existing pathology laboratory information systems, and computer storage to store the digital data.
- Reticence of soon-to-retire pathologist shareholders in their group to support the financial investment necessary to acquire and deploy digital pathology in their practice.
- Opposition to "going digital" by the older generations of pathologists who want to continue using their light microscopes in daily clinical practice.
- Concerns about the possibility that the chosen digital pathology vendor might be acquired or even stop supporting its DP systems in downstream years.
- The lack of a universal standard for scanning glass slides comparable to the DICOM standard used for radiology images. The scanners from different manufacturers use different formats to produce whole slide images.
- Closed digital pathology systems that are engineered to only read the manufacturer's digital scan format. TDR

FDA's Regulatory Path for Pathology AI Algorithms

ARTIFICIAL INTELLIGENCE (AI) IS PREDICTED TO BE TRANSFORMATIONAL IN DIAGNOSTICS IN COMING YEARS. The underlying technologies are being developed at a swift pace and last year the federal **Food and Drug Administration** (FDA) took steps to define these algorithms as medical devices.

On Feb. 2, 2023, the FDA issued the rule "Medical Devices; Hematology and Pathology Devices; Classification of the Software Algorithm Device to Assist Users in Digital Pathology." The FDA summarized the rule as follows:

> *The Food and Drug Administration (FDA, Agency, or we) is classifying the software algorithm device to assist users in digital pathology into class II (special controls). The special controls that apply to the device type are identified in this order and will be part of the codified language for the software algorithm device to assist users in digital pathology's classification. We are taking this action because we have determined that classifying the device into class II (special controls) will provide a reasonable assurance of safety and effectiveness of the device. We believe this action will also enhance patients' access to beneficial innovative devices.*

In this final rule the FDA referenced that, on Dec. 31, 2020, it had received **Paige.AI, Inc.'s** request for De Novo classification of Paige Prostate. FDA reviewed the request to classify the device under the criteria for classification set forth in section 513(a)(1) of the Food Drug & Cosmetics Act. Defined as a Class II device, the federal agency cleared Paige Prostate for clinical use on Sept. 21, 2021.

Why Many Pathologists Are Cautious about Digital Path

Mid-sized and smaller pathology groups often watch and wait to see what works, what doesn't

CEO SUMMARY: In many major academic centers and the nation's largest regional pathology supergroups, use of whole slide images and digital pathology workflow are accepted and established. This is often because of benefits unsupported by a pure return on investment. The clinical gains outweigh the capital costs. But for smaller-sized pathology groups, the capital cost of a digital pathology investment must show a robust return on investment, for reasons described below.

PART ONE

WHEN IDENTIFYING THE FACTORS CURRENTLY IMPEDING SPEEDIER ADOPTION of fully digital pathology systems by many of the nation's mid-sized and smaller pathology laboratories, it is necessary to look at the buyer's side of the equation.

Market uptake on digital pathology (DP) systems has been slow for reasons familiar to pathologists and the professionals who work most closely with them. Clients and regular readers should keep in mind that the descriptions that follow are broad generalizations. Given the unique mix of personalities in every pathology group practice, some combination of these factors probably play a role in decisions to defer buying DP systems.

Thorough, Thoughtful

First: across the pathology profession it is accepted that pathologists are thorough and thoughtful when making decisions about the structure of their lab's finances, operations, and clinical service mix. That thoroughness means it can take months—even years—for an individual pathologist within a group practice to align with either a "yes we will buy" or "no we won't buy at this time" decision. This attribute of pathology group practices greatly frustrates companies selling DP products and services.

Second: at this time there seems to be no compelling business case and return on investment (ROI) model that demonstrates how mid-sized and smaller pathology laboratories can implement a full DP workflow solution and get their investment back in a reasonable period of time.

Major Investment Required

Third: the expense of going "fully digital" for many pathology groups is a major investment. Data published by research companies indicate that—for a mid-sized pathology group—an investment of between $150,000 to $600,000 is required just for a basic DP installation, and that the investment can be substantially more depending on the objectives of the pathology laboratory.

But historically, pathology groups have not had large capital budgets for

investments, unlike radiologists for example who must acquire imaging systems that cost millions of dollars. Thus, pathology groups do not have an established pattern of funding significant and ongoing capital expenditures. For this reason, the decision to invest in a full digital pathology system typically faces resistance from some partners and shareholders in the pathology lab. Vendors selling DP systems have to overcome this resistance. *(See sidebar.)*

Approaching Retirement

Fourth: the internal dynamics of many pathology group practices and pathology laboratories create inertia to avoid making the decision to spend the capital required to "go digital."

Bluntly stated, in many of these group settings, the controlling shareholders are Baby Boomer pathologists approaching retirement. The younger pathologists are often on salary and working on a partner track.

It is regularly observed that the Baby Boomer pathologists would rather optimize their annual compensation within the group during their remaining years. They don't want to reduce their profit distribution in coming years to buy the DP system because it won't benefit them directly after retirement.

'I Like My Light Microscope!'

Fifth: DP vendors recognize that one barrier to adoption of digital pathology in mid-sized and smaller group settings is the resistance of older pathologists to give up their light microscopes and transition to viewing cases on a monitor. This factor is in play when a pathology group practice conducts its internal debate about when and how to adopt digital pathology.

If there is a wild card in this deck, it is the fact that, for nearly 15 years, residency and fellowship programs have used digital images and WSIs to train the up-and-coming pathologists. Now in clinical practice, these are the pathologists who are comfortable working digitally.

These younger pathologists are the future of the profession and they want to practice pathology using WSIs and the AI-powered image analysis solutions now coming to market. This is the group of pathologists eager and ready to bring full digital pathology systems into their labs. TDR

Is Lack of Access to Capital an Impediment?

TWO FACTORS CLEARLY HAVE A ROLE IN RETARDING THE FASTER ADOPTION of fully digital pathology solutions by the nation's mid-sized and smaller pathology group practices and laboratories.

One factor is the lack of a business case that demonstrates a compelling return on investment (ROI) for adopting a full digital pathology (DP) system. This objection is heard regularly from business leaders in different pathology groups.

The second factor compounds the first. It is the fact that pathology laboratories historically have not had substantial capital spending needs. Aside from equipment for the histology laboratory, the professional component of surgical pathology typically required light microscopes and a pathology laboratory information system (LIS).

That is not the case when implementing a full DP system across the entire pathology practice. Pathologists need an upfront capital investment of at least $200,000 for the basics to as much as $1 million for a comprehensive digital pathology transformation.

For comparison, radiology group practices for decades have recognized the need for substantial capital spending to keep their practice at the cutting edge of imaging technologies. They regularly buy and deploy imaging machines that cost $1 million or more.

Pioneering DP Companies Ended Up Being Acquired

Between 2000 and 2020, new owners took control of four of five digital pathology firms

CEO SUMMARY: One reason why the adoption of a full digital pathology solution has lagged behind expectations may be attributed to the fact that four of the pioneering companies did not survive as independent businesses. They were sold and not all the new owners continued investing and developing those DP systems. This was watched by pathologists across the nation and made some of them wary of going "full digital pathology" and then getting stuck with a sunsetted DP system down the road.

PART TWO

Is it significant that, of five companies that entered the digital pathology market between 2000 and 2020, all but one were acquired?

This may be another reason why there is uncertainty today in the U.S. market for scanners and digital pathology (DP) workflow solutions. Many pathologists—recognized as inherently deliberative and conservative in how they make business decisions—have legitimate concerns about whether the DP vendor they chose will be around after their pathology group begins using its digital pathology systems.

New Owners of DP Firms

Pathologists have watched as a number of the leading digital pathology companies were acquired by larger corporations. Sometimes the new owners slowed development of these DP products. In two cases, post-acquisition, the new buyers sunsetted those DP products and stopped upgrading them and servicing them.

This frustrated pathology groups using these products because they did not get important updates and valuable new features as technologies improved.

A survey of these five major companies that were early to market with a complete digital pathology system shows that only one survives today in its original corporate structure.

'Total Digital Path' Solution

In the following survey, The Dark Report describes the best-known pioneering companies that sold a "total digital pathology solution." Starting in the 2000s, these companies delivered a complete package that included scanners, monitors, and software to allow the pathology laboratory to install the hardware, interface to the pathology LIS, and handle workflow.

Today, the field of digital pathology has a growing number of companies. Most offer targeted solutions, not a comprehensive digital pathology solution. One characteristic of this recent (post-2020) class of DP companies is that their mission statements center upon developing and delivering digital image analysis solutions that incorporate artificial intel-

ligence and related technologies. *(See Part Three, pages 11-14.)*

Early DP Entrants

Below is a list of five of the better-known early entrants that many consider the pioneers in digital pathology. Each sold a complete package of digital pathology equipment and software:

- **Aperio Technologies** was founded in San Diego in 1999 by CEO Dirk Soenksen. The company sold its first digital pathology system in 2001. Over the next decade, it regularly placed digital pathology systems, mainly in academic center pathology laboratories and the larger regional pathology groups.
- **BioImagene** of Sunnyvale, Calif., launched in 2003 with founders Mohan Uttarwar and Ajit Singh, PhD. It sold its first digital pathology system in 2007.
- **Omnyx** of Pittsburgh, Penn., was created in 2008 by **University of Pittsburgh Medical Center** (UPMC) and **GE Healthcare**, a division of **General Electric**. This well-financed competitor was immediately considered a challenger to then-market leader Aperio.
- **Inspirata** of Tampa, Fla., was founded in 2014 by Satish K. Sanan. It was based on technology developed at **Moffatt Cancer Center** by Mark Lloyd, PhD.
- **Philips** of Amsterdam, The Netherlands, introduced the first FDA-cleared FDA digital pathology system in the United States in 2017.

DP's Frontrunners

In the years 2000 through 2020, the companies above were considered the frontrunners in selling complete digital pathology solutions to pathology labs in the United States.

Returning to the point that many pathology group practices have seen digital pathology companies come and go, here is what happened to those early digital pathology pioneers:

- Aperio Technologies was acquired in 2012 by **Leica Biosystems**, a division of **Danaher Corporation**. Leica continues to develop and support this product.
- BioImagene was acquired in 2010 by **Ventana Medical Systems**, a division of the **Roche Group**. It has been rebranded as the Roche Digital Pathology system.
- Omnyx assets were sold to Inspirata in January, 2018.
- Inspirata's digital pathology system assets were sold to **Fujifilm** in January, 2023. Inspirata continues today as a self-described oncology informatics company.

Philips DP Survives 1st Wave

Of the five companies discussed here that launched in the United States prior to 2020 and offered a complete digital pathology solution, only Philips continues to own, sell, and service the DP products it has sold for clinical use in the United States since clearance by the FDA in 2017.

The experience of these early digital pathology companies coming to market—only to be acquired by new owners within a short number of years—has not gone unnoticed by pathologists in this country. It gives them a reason to be wary.

Another relevant factor is that each of these five early entrants selling a full DP system had marquee pathology lab clients who frequently spoke at clinical laboratory conferences about their successes and setbacks in their roles as groundbreakers for the full adoption of digital pathology in daily clinical care.

Of course, when things did not go well at those marquee labs, pathologists throughout the country would hear the gossip. The problems and the sale of these companies were red flags and had a role in waving off some pathology groups from deciding to invest in a complete digital pathology solution. TDR

Fitting Pathology AI Firms into DP Market Puzzle

Pathology AI companies need wider adoption of digital pathology before sales can increase

CEO SUMMARY: Today, the best-known developers of AI-based algorithms have been in business almost 10 years. During that time, there has been continuous improvement in the digital technologies used in digital scanning and digital image analysis. Despite these improvements, many pathology group practices have yet to make the commitment to acquire and deploy a full digital pathology system in their labs. This limits the opportunity for pathology AI companies to increase sales.

PART THREE

IMAGE ANALYSIS IS THE NEWEST CATEGORY OF DIGITAL PATHOLOGY SOLUTIONS to reach the market. Numerous companies launched during the past 10 years with the stated goal of bringing digital image analysis solutions to market.

What goes unremarked is that when today's best-known pathology AI companies launched in the mid-2010s, their initial target was to sell solutions to the research market because FDA review and clearance is required for products intended for use in patient care.

First Customers for Path AI

Moreover, pharma, clinical trials, biotech, and the scientific community were hungry for solutions that would make the analysis of digital tissue images faster, more accurate, and less time-intensive for pathologists reading those images. These entities also had funding to acquire and use artificial intelligence (AI)-powered image analysis algorithms.

Another reason why, at inception, these companies targeted non-clinical buyers is that every AI-powered algorithm must be trained with huge amounts of data. These nascent pathology AI companies saw the opportunity to work with the research community and gain access to the pathology cases they could use to train their algorithms. They also collaborated with major hospitals and academic centers to access pathology cases they could use to train their AI products.

Given these facts about the state of artificial intelligence technologies in the mid-2010s, emerging anatomic pathology AI companies needed to achieve three things to succeed and earn profits for their investors.

First: They needed access to large volumes of pathology cases to train their AI algorithms.

Second: They needed cash flow as soon as possible, another reason why they concentrated sales and marketing on the research community.

Third: Before they could successfully sell AI-powered digital analysis algorithms to the nation's anatomic pathologists, they needed pathology group practices and pathology labs to be using digital

pathology, with scanners and pathologist workflow solutions in daily use. To use an AI algorithm, any lab customer must be using whole slide images (WSIs).

Another Piece in the Puzzle

As the companies offering AI algorithms entered the market, they added another piece to the puzzle of when the market for all things digital pathology expands to the point where all digital pathology vendors have adequate sales to move them from red ink during their market launch phase to black ink as a viable and ongoing business.

The holy grail—and ultimate objective—of the development efforts of this class of pathology AI companies is to produce what we shall describe as "AI-powered digital image analytical tools" that can take a whole slide image, analyze it, and deliver a diagnosis with accuracy and precision comparable to a trained pathologist.

The AI algorithm sector today has plenty of aspiring companies. Currently, the website of the **Digital Pathology Association** (DPA) lists 29 companies under the vendor category of AI.

The primary and ultimate goal of this class of companies is to use such technologies as artificial intelligence (AI), machine learning (ML), deep learning (DL), natural language processing (NLP), and neural networks (NL) to give pathologists tools that analyze whole slide images.

Submitting to FDA for Review

As noted earlier, these firms have made their first sales inroads with the pharmaceutical, bioresearch, and clinical trials sectors. They are waiting for the right moment to submit their AI systems to the federal **Food and Drug Administration** for review and clearance for use in clinical care settings.

This part three looks at the current state of the market for these pathology image analysis systems. It is based on developments at the handful of pathology AI companies that regularly issue press releases and have their executives speak often at lab industry conferences.

Over the past 10 years, investors poured more than $1 billion into pathology AI companies, as shown in the sidebar on page 13. Typically the first customers for these companies have been the nation's largest pathology organizations. They have the budgets and the scale to buy these AI-powered image analysis algorithms and try them out.

As of today, most of the nation's anatomic pathology organizations with a significant volume of case referrals are using whole slide images and digital pathology workflow for many of their cases. It is equally true that these same organizations are the first buyers of the AI-powered image analysis offerings.

Positive Reviews for Path AI

These early adopter pathology laboratories report favorable results from both the use of digital pathology workflow and the use of the specific AI image analysis algorithms that they introduced into daily workflow. Typically, these algorithms are used for analyzing specific types of cancer and other diseases. For this reason, these early adopter lab organizations currently use AI for only a portion of their cases.

Meanwhile, the majority of the nation's pathology groups and pathology labs seem to have a watch-and-wait approach. They are cognizant that there is a cost to use these AI solutions, along with the challenge of getting reimbursed by payers.

As noted in part one, another factor is that there are pathologists who continue to resist moving from their light microscopes to a digital pathology workflow. That attitude retards the ability of pathology AI companies to sell more product.

Collectively, these market factors are what Wall Street analysts and investors like

Big Money Made Big Bets on the Potential for Artificial Intelligence to Transform Pathology

BETWEEN DECEMBER 2020 AND MAY 2021, FOUR AI PATHOLOGY COMPANIES raised a collective total of $326 million from private equity firms. Investors were gung ho on the potential of AI to transform pathology and produce streams of revenue.

But that is not the whole story. Each of these four companies raised capital in multiple rounds of financing. Pathologists considering when and how to bring AI-powered image analysis solutions into their group practices may find it useful to understand how much investor money is fueling the race to introduce AI-powered algorithms into daily clinical practice. Here is a snapshot of the capital invested in these four companies.

During early 2021, the four companies were financed as follows:

• Proscia, Dec. 2020 *(Series B round)*	$23 million
• Ibex, Mar. 2021 *(Series B round)*	$38 million
• Paige.AI, Jan. 2021 *(Series B round)*	$100 million
• PathAI, May 2021 *(Series C round)*	$165 million
Total over six months:	$326 million

Total Investments in Path AI

Here are snapshots of these same four pathology AI companies showing their founding years and total capital invested to date:

PROSCIA, founded in 2014. In seven rounds of funding it raised a total of $80.5 million. Its latest funding was raised on January 11, 2024, from a Series C round.

PAIGE.AI, founded in 2017. In five rounds of funding it raised a total of $220 million. Its latest funding was a Series C round of $100 million raised on January 14, 2021.

IBEX MEDICAL ANALYTICS, founded in 2016. In seven funding rounds it raised a total of $118.5 million. Its latest funding was a Series C round of $55 million, closed on Sept. 6, 2023.

PATHAI, founded in 2016. In six funding rounds it raised a total of $355.2 million. Its latest funding was $100 million on Jan. 1, 2022, from a debt financing.

Adding to these numbers, a total of $774.2 million dollars has been invested in these four companies in the past 10 years. That's three-quarters of a billion dollars.

to describe as "headwinds." They use this term to describe the market dynamics that are keeping the companies they track from achieving goals for increased revenue, net profit, and expanded market share.

The consequences of "headwinds" are showing up in what we will call the "Class of 2021" pathology AIs. These four companies received a collective third of a billion dollars in investments in just the first five months of 2021. *(See sidebar above, "Big Money Made Big Bets on the Potential for Artificial Intelligence to Transform Pathology.")*

The companies and the year they were founded are:

- **Ibex Medical Analytics**, 2016
- **Paige.AI**, 2017
- **PathAI**, 2016
- **Proscia**, 2014

Each of these companies took a different path to access the huge volume of pathology slides required to train their AI. Israel-based Ibex works closely with **Maccabi Healthcare Services** and other pathology laboratories in Europe and other countries. Its website says it used 10 million slides to train its AI.

Paige.AI was created by a group from inside **Memorial Sloan Kettering Cancer Center** (MSK) and used MSK's slide archives to train its AI.

PathAI's website states that it used "data from more than 15 million annotations" to train its AI. Also, in July 2021, it acquired the national pathology company, **Poplar Health**, based in Memphis, Tenn. This gave PathAI access to more than 20 decades of cases and glass slides—along with current incoming cases that it could use to train its AI.

At Proscia, its access to pharma and bioscience pathology cases was the early source of material with which to train its AI. In 2020, it signed an agreement with the armed force's **Joint Pathology Center** to digitize more than 100 years of glass slides. This gave Proscia access to 55 million glass slides—the world's largest archives of pathology slides and a bonanza for the training of Proscia's pathology AI algorithms.

Path Forward for AI Firms

The path forward for pathology AI algorithm companies is challenging. In order for them to make more sales and generate enough revenue to reward their investors, they need pathology groups and pathology labs here in the United States and abroad to install scanners and digital pathology systems.

The experience of the past 20 years is evidence that adoption of digital pathology systems will continue at a measured pace, at best. This does not bode well for the pathology AI companies whose investors want results in the form of strong growth and profits for distribution to stockholders.

There is a reality that is seldom discussed in this field. As noted in the earlier parts of this intelligence briefing, each year, meetings like the **Digital Pathology Association** and the **Digital Pathology Congress-Europe** have increasing attendance and speakers who are enthusiastic about the benefits of digital pathology. This optimism is not often tempered by assessment of the digital pathology marketplace from the perspective of "push versus pull."

This is a recognized dynamic associated with every new product and every new company. The "push" side means that, as the company or product hits the market, the target customers do not react enthusiastically and in large numbers.

'Push' vs. 'Pull' Market

Consequently, a company spends considerable money and effort to put its product in front of potential buyers. For example, when everyone has smartphones and Android and iPhone are the established market leaders, any company launching a new line of smartphones will be required to "push" that product to get customers to pay attention and eventually make a purchase.

Compare that to the "pull" side. This is where a company introduces a product that consumers find irresistible. The target customers rush to buy it.

One example of a pull success is **eBay**. When it launched in 1995 (as **AuctionWeb**), eBay gave small sellers access to a huge market. It made it possible for buyers to find almost anything imaginable at a reasonable price. Steve Jobs' introduction of the first smartphone—the **Apple** iPhone—enjoyed the same instant and spectacular sales growth. People rushed to trade in their flip phones and get an iphone.

Within this framework, the evidence is obvious that digital pathology is a "push" market. Every vendor in every category puts major effort into every sale. The sales cycle for a lab to decide to go digital can be months, even years, before it signs a purchase agreement.

Accept this truth—and the inadequate reimbursement for DP services—and the pace of pathologist's adoption of DP will probably match the past decade. TDR

Regulatory Update

Assessing the Clinical Service & Revenue Issues of the LDT Rule

Clinical labs must understand cost-benefits of their LDT offerings as they prepare for FDA compliance

BARRING INTERVENTION BY FEDERAL COURTS OR THE **U.S. CONGRESS**, clinical laboratories will have to comply with the **U.S. Food and Drug Administration's** (FDA) new final rule regarding laboratory developed tests (LDTs).

To do so, many laboratories will need to take a hard look at their current LDT offerings, with an eye toward which ones are most likely to generate revenue. They will also have to think more strategically about how they deploy LDTs and how they position themselves in the marketplace. That's the word from Valerie Palmieri, CEO and founder of **Momentum Consulting**, which advises companies involved in diagnostic manufacturing and services.

As THE DARK REPORT has noted, the FDA is phasing out its so-called "enforcement discretion" approach to LDTs in five stages over a four-year period, beginning May 6, 2025. With that comes a host of requirements for reporting, labeling, registration, and, in many cases, premarket review of LDTs. *(See TDR, "What Labs with LDTs Must Do to Comply with FDA's LDT Rule," July 22, 2024.)*

"The rule is going to affect clinical care," Palmieri told THE DARK REPORT. "It's going to affect the revenue and profitability of labs performing LDTs. Labs must prioritize the tests into what they want to keep and what they will be forced to outsource. In fact, labs must be as skilled at outsourcing as they are at keeping LDTs in-house, because there will probably be LDTs they won't take through the regulatory process."

This is all happening, she said, as labs deal with existing constraints, including a shortage of labs techs and pressure to reduce prices. "Labs are forced to do more with less and the LDT rule adds a burden on the system within a specific time frame," she said.

Adjusting Lab Operations

Palmieri outlined five key points that laboratories will have to consider as they adjust their operations to accommodate the rule.

First: Labs need an "end-in-mind strategy," she said. Do they have an exit plan for their business? Should they consider an IPO or M&A strategy? How do they build their lab business for sustainability and minimize rework?

Second: "Labs should build a three-year financial plan for their exit strategy," she said. "It needs to be more than a one- or two-year plan, and a five-year plan won't be realistic." At this stage, labs need to consider the cost and benefits of keeping LDTs in-house versus outsourcing, she added. "Labs will face a teeter-totter of costs going up and potentially prices coming down."

Labs should identify the LDTs that deliver "high enterprise value, such as rare disease tests with strong intellectual property," she said. "What are the value drivers? What makes the lab different?"

Third: Palmieri advises that once the lab figures out which LDTs it is keeping, it must operationalize the following three-part plan to implement these LDTs within the new regulatory framework:

- Determine the QMS (quality management system) foundation, including ISO, **CAP**, and CLIA requirements.
- Address clinical data gaps in the LDTs. For example, she said, a lab might want to take a test offered in a local region and make it available nationally, which may require the lab to calibrate the test for a broader population. "One of the biggest gaps will be validation demographics," she said. "We are not a homogeneous population. We could be using LDTs to make decisions on people's health outside the specific population for which it was validated."
- Address staffing issues. "Once the lab determines the LDTs it's keeping and the LDTs it's shedding, it needs to understand the competency of its team," she said. For example, "Does the lab need to bolster the QMS team? Does it need to bring in consultants?"

Fourth: Labs should assign its LDTs to three group categories: High Margin, Export Plan, and Import Plan.

Fifth: The lab should reconfirm the model and identify the biggest risks in the LDT menu as well as upsides and downsides in the new model. The lab should also consider ways to mitigate the downsides.

Forced Efficiencies

All told, the LDT rule "is going to force efficiencies on the system, because labs don't have other choices," Palmieri noted. "It will also have an impact on clinical decision-making. It might force more use of AI and more use of extenders within a laboratory versus technologists."

A critical deadline, she said, will come in May 2026, when labs are required to register their LDTs. "The lab will give the FDA the IFU (instructions for use). FDA will know the lab's competitors. It's going to check the labeling."

Palmieri noted that genetic tests registered with **Medicare's** MolDX program may be "ahead of the curve" when it comes to FDA scrutiny. However, "MolDX is focused on clinical utility and outcomes," she said. "The FDA is focused on safety and efficacy."

Market Review Exemption

"Labs should bear in mind that most new LDTs put on the market after May 6, 2024, will be subject to the full regulatory framework," she explained. "LDTs marketed prior to that date will be exempted from premarket review and most quality system requirements, provided that the performing laboratories do not make substantial changes to the LDTs."

One point Palmieri emphasized is that the exemptions in the rule are not grandfather clauses. Labs must still register LDTs placed on the market prior to the cutoff date and must comply with other requirements.

"The sooner labs start riding this bike within their organizations, the better," she advised. "If a lab is on a January to December budget, it needs to understand what it may lose from its top revenue-producing LDTs in 2025."

Palmieri will discuss these topics in detail during a special DARK INTELLIGENCE GROUP webinar, "FDA's LDT Rule: Understanding What's Compulsory, What's Not," scheduled for Sept. 12 at 1pm Eastern time. She'll be joined by two other presenters: Jane Pine Wood, JD, an attorney with **McDonald Hopkins'** national Healthcare Practice Group, and Sheila Walcoff, JD, CEO and founder of **Goldbug Strategies** LLC.

The FDA expects labs to be in compliance by May 6, 2025, followed by other compliance requirements for 2026 and 2027. This webinar is a "must attend" for you and key members of your team. TDR

Lab Market Update

Federal Court Issues Ban on FTC's Noncompete Rule

Judge's decision stops the FTC from enforcing the rule against any company nationwide.

By now, most clinical lab managers and pathology practice administrators are aware of the **Federal Trade Commission** (FTC) rule that bans noncompete agreements in virtually all employment contracts in the United States. The final rule was to take effect on Sept. 4, 2024, and applies to most private, for-profit business entities, which includes most clinical laboratories.

The new development is that on Aug. 20, 2024, The **Northern District of Texas** in *Ryan, LLC v. FTC*, granted the Plaintiff-Intervenors' motion for summary judgment. The judge in this case ruled that the FTC's noncompete rule is unlawful, and issued an order that the FTC's noncompete rule shall not take effect on September 4, 2024, or thereafter. There was a preliminary injunction which ruled in favor of the specific plaintiffs. By contrast, this ruling stops the FTC from enforcing the rule against any company nationwide.

FDA's Rulemaking Authority

Another aspect of this ruling is that—besides blocking the federal agency from enforcing the noncompete rule—the court held that the FTC lacks any substantive rulemaking authority with respect to unfair methods of competition. The FTC does have the right to appeal. If it did, this appeal would be heard by the **U.S. Court of Appeals for the Fifth Circuit**.

In the noncompete rule, the FTC rule defines a "business entity" as "a partnership, corporation, association, limited liability company or other legal entity, or a division or subsidiary thereof." *Investopedia* defines a noncompete as "a legal agreement or clause in a contract specifying that an employee must not enter into competition with an employer after the employment period is over. These agreements also prohibit the employee from revealing proprietary information or secrets to any other parties during or after employment."

Workers required to sign noncompete agreements may include contractors and consultants as well as payroll employees. According to an April 23 FTC press release, the noncompete rule will generate new businesses, raise worker wages, lower healthcare costs, boost innovation and protect the fundamental freedom of workers to change jobs.

The FTC projected the final rule would grow new business formation by 2.7% per year and result in higher earnings for workers. The rule was also expected to lower healthcare costs by up to $194 billion and produce 17,000 to 29,000 more patents per year over the next 10 years.

Noncompete Agreements

According to the FTC rule, the "ban applies to a term or condition of employment that prohibits a worker from, penalizes a worker for, or functions to prevent a worker from:

- "Seeking or accepting work in the United States where such work would begin after the conclusion of the employment," and,

- "Operating a business in the United States after the conclusion of the employment."

The FTC issued its proposed rule in January 2023 with a 90-day public comment period. Over 26,000 comments were received and almost all of those were supportive of the recommended ban on noncompetes. The FTC made changes to the final rule after carefully reviewing the received comments and voted 3-2 in favor of the ban.

"Noncompetes block workers from freely switching jobs, depriving them of higher wages and better working conditions, and depriving businesses of a talent pool that they need to build and expand," said FDA Chair Lina Khan, JD. "By ending this practice, the FTC's proposed rule would promote greater dynamism, innovation, and healthy competition."

Noncompetes Hurt Market

One example given by the FTC involved a geneticist at a university creating a biotech startup to develop immunotherapies. The FTC stated this individual should not have a noncompete agreement because it artificially creates scarcity and suppresses a market for top scientific talent.

The FTC affirmed that employers already have options to noncompetes, such as trade secret laws and non-disclosure agreements (NDAs), that are intended to protect proprietary and sensitive information. According to the FTC press release, over 95% of employees with a noncompete also have an NDA in place.

As written, the FDA's final rule stated that existing noncompete agreements for senior executives could remain in place, but employers would be prohibited from introducing or enforcing new noncompetes. Senior executives are defined as workers earning more than $151,164 annually who have policy-making functions. The FTC estimates those who qualify as senior executives make up less than 0.75% of the workforce.

The FTC spent extensive time discussing the fact that there are workers earning high wages who may have titles and job responsibilities but who are not senior executives. Some of those individuals still face exploitation and coercion from noncompete agreements and do not generally bargain over them. The FTC wanted to make certain those workers were excluded from noncompetes, so they developed a two-tiered test regarding salary and policy-making authority.

A policy-making worker is someone who has control over a significant aspect of the business entity and can make decisions without approval from a person at a higher level.

Had the FTC's noncompete rule become effective on Sept. 4, 2024, all clinical laboratories would have needed to take the following steps:

- Determine who is a senior executive.
- Realize the noncompete ban likely applies to the sales and marketing departments.
- Be cognizant the ban likely applies to scientists and other highly trained individuals within the laboratory.
- Recognize that the FTC views department heads or other highly paid, non-C-suite employees to not have sufficient bargaining power to avoid exploitation and coercion.

Public entities, not for profit entities, and other industry distinct entities excluded under the jurisdiction of the FTC are not covered under the noncompete ban.

Noncompetes and NDAs have been part of standard business practices for many years. It is recommended that clinical laboratory managers and pathology practice administrators consult with their legal advisors to understand the consequences of the Aug. 24, 2024, court ruling. It is also advisable to watch to see if the FTC chooses to file an appeal with the Fifth Circuit Court. TDR

INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

To challenge the federal **Food and Drug Administration** (FDA) final rule on laboratory developed tests (LDTs,) the **Association for Molecular Pathology** (AMP) filed a lawsuit on August 20, 2024, in the **United States District Court for the Southern District of Texas**. This is the second lab industry lawsuit challenging the LDT rule to be filed against the **Department of Health and Human Services** (HHS). The AMP lawsuit focuses on the issues that directly affect clinical laboratories in academic medical centers. The co-plaintiff in the lawsuit with AMP is pathologist Michael LaPosata, MD, PhD, Professor and Chair of the Department of Pathology at the **University of Texas Medical Branch-Galveston**.

MORE ON: *LDT Lawsuit*

The first lawsuit challenging the LDT rule was filed on May 29, 2024, by the **American Clinical Laboratory Association** (ACLA) and its member company, **HealthTrackRx** in the **United States District Court for the Eastern District of Texas**. Both lawsuits assert that the FDA does not have the authority to regulate LDTs.

BIG RANSOMWARE ATTACK HITS UK LAB

On June 3, 2024, a ransomware attack hit the clinical laboratory service provider of several major London hospitals. As reported by *Bloomberg*, the cyberattack targeted **Synnovis**, a medical testing company based in Europe that manages the laboratories of **Guy's and St Thomas' NHS Foundation Trust**, and **King's College Hospitals NHS Trust**. The ransomware attack disrupted Synnovis' lab test services to multiple hospitals, general practioner (GP) clinics, and blood banking services in the region. Synnovis said that its capacity to process samples was "significantly reduced" and that it was farming out non-urgent work to other pathology labs. Elective surgeries and GP appointments were canceled because of the ransomware attack. *Bloomberg* reported that there was "an emergency call for ... blood donations, and at least 1,100 operations were ... rescheduled ... due to delays caused by the cyberattack."

TRANSITIONS

- Kwami Edwards is the new Chief Operating Officer at Lincoln, Neb.-based **Telcor, Inc.** Edwards previously served with the **Courtyard Group** and **Memorial Sloan-Kettering Cancer Center**.

- **Paige** of New York City announced the appointment of Razik Yousfi to the position of CEO and Chief Technology Officer. He had been Paige's Senior Vice President of Technology. Yousfi previously held positions with **HeartFlow**, **Systran**, and **Siemens**.

- **Bio-Rad Laboratories** of Hercules, Calif., named Jon DiVincenzo as President and CEO. His prior positions were with **Labcorp**, **Covance**, **PerkinElmer**, **Enzymatics**, **Merck**, **EMD Millipore**, and **General Electric**.

That's all the insider intelligence for this report.
Look for the next briefing on Monday, September 23, 2024.

Publisher: Robert L. Michel *rmichel@darkreport.com*
Executive Publisher: Bob Croce *bcroce@darkreport.com*
Managing Editor: Michael McBride *me@michaelmcbride.com*
IVD Reporter: Donna Pocius *donna11019@att.net*
Legal/Compliance Reporter: Stephen Beale *sbeale58@gmail.com*
Regulatory Reporter: Jillia Schlingman *jpschlingman@yahoo.com*

Register Today! Don't miss out!

★SPECIAL WEBINAR!★

FDA's LDT RULE: Understanding What's Compulsory, What's Not

Protect Your Lab's Essential LDTs! Assess the Financial Impact!

Webinar: SEPTEMBER 12 @ 1:00 PM EDT

Every lab with laboratory developed tests (LDTs) now faces a complex path to comply with the final FDA LDT rule. Complicating your lab's compliance is the uncertainty in the rule's interpretation.

To help you and your team stay ahead of the LDT rule deadlines, we've assembled a top-flight panel of the lab industry's recognized experts for this special webinar. Our experts will provide you understanding and context for the requirements of the LDT rule. You'll get invaluable insight, recommendations, and admonitions about compliance.

Best of all, our interactive webinar format allows you and your team to interact with these experts during the webinar. You'll gain the essential knowledge you need to assess existing LDTs, prioritize your compliance steps, and protect the income stream produced today by your existing LDTs!

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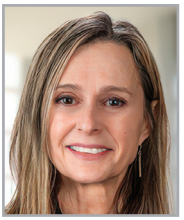

Jane Pine Wood, JD

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UPCOMING...

- ***Association of Molecular Pathology sues Feds in second court case challenging FDA LDT rule.***
- ***Can phlebotomy be automated? One company says 'yes' and has EU mark to begin selling its solution.***
- ***Latest Kaufman Hall Report finds that 40% of 1,300 U.S. hospitals studied are losing money.***

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