NOVEMBER 2019 # 60

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Special Issue: *Digital Pathology*

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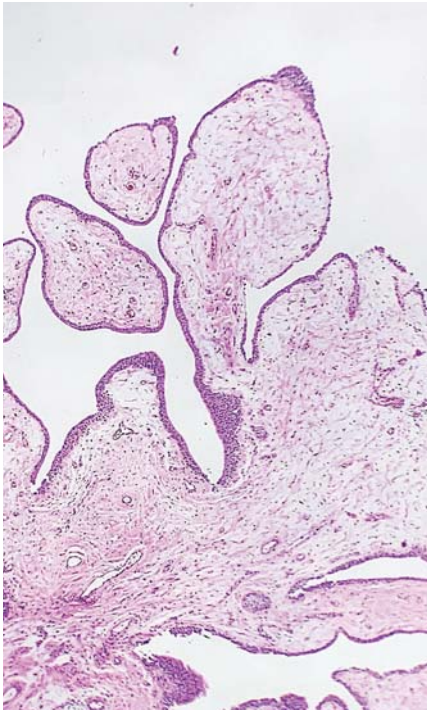
ThermoFisher SCIENTIFIC

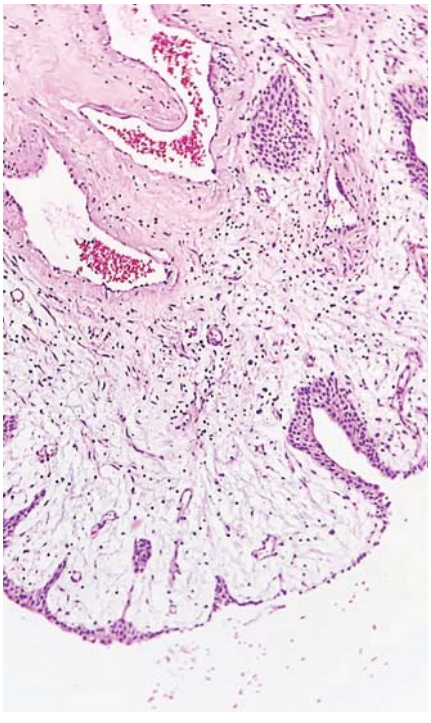
Case of the Month

A 51-year-old man presented with a two-month history of gross hematuria without any other symptoms. Ureteroscopy showed a 1.5 cm polypoid mass that was completely excised and sent for histopathologic examination.

What is your diagnosis?

- *A* Urothelial papilloma
- *B* Inflammatory polyp
- *C* Inverted papilloma
- *D* Fibroepithelial polyp
- *E* Florid cystitis cystica/ glandularis





Answer to last issue's Case of the Month…

A. Multiple endocrine neoplasia type I

The image is of is a pancreatic neuroendocrine tumor, a neoplasm found in approximately 60 percent of patients with multiple endocrine neoplasia type I (MEN I). Such tumors also occur in 5–15 percent of patients with von Hippel-Lindau syndrome and occasionally in patients with neurofibromatosis type I. They are not a feature of MEN II.

To register your guess, please go to http://tp.txp.to/1119/case-of-the-month
We will reveal the answer in next month's issue!

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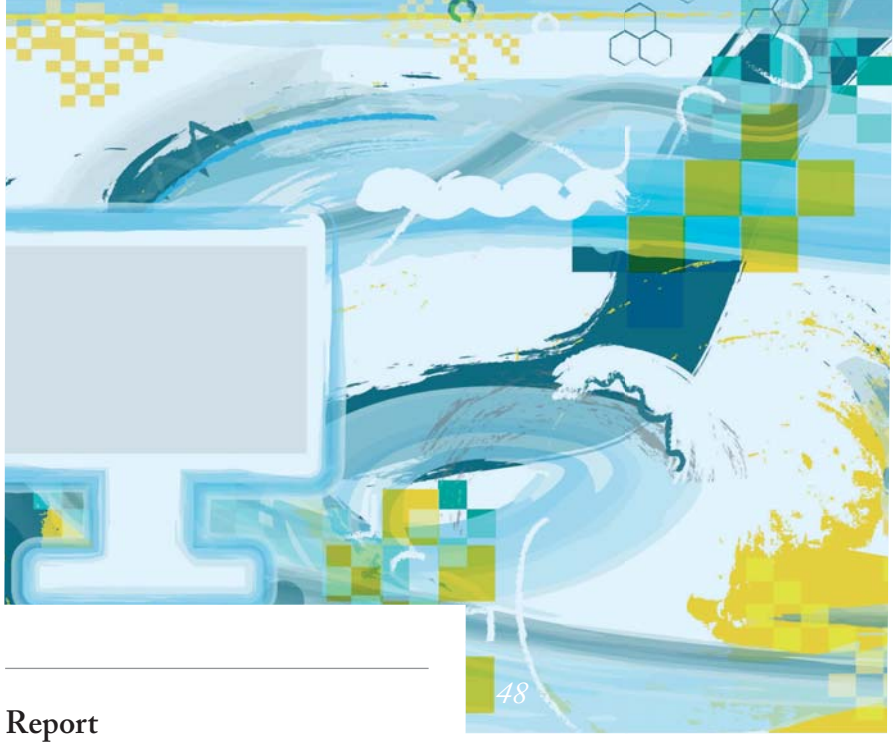
Pathology resources vary around the world – but technology can help



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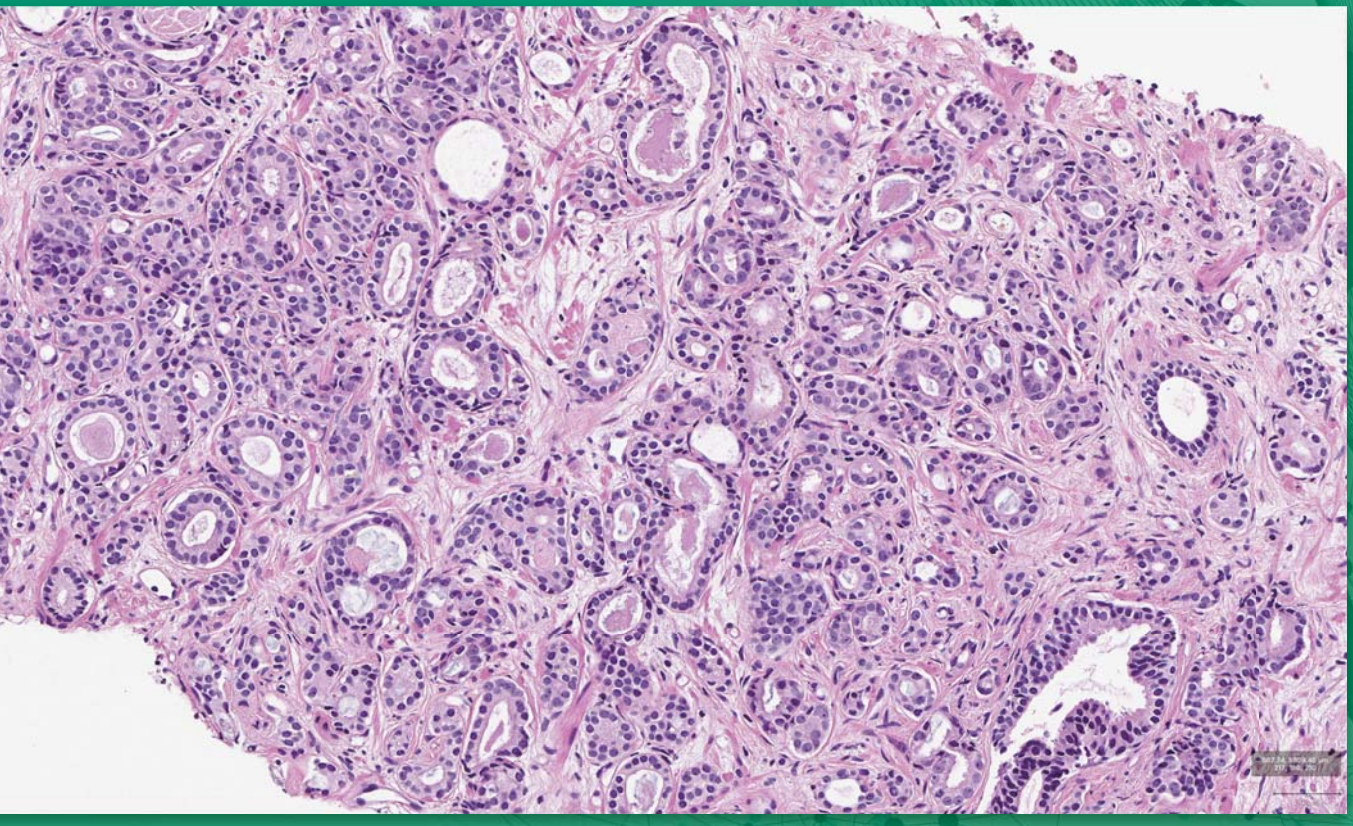
TRY THIS!

WHAT IS YOUR **GLEASON SCORE?**



To compare your score with AI, check page 11.

DeepDx

DeepDx is a platform for AI-assisted digital pathology. The modules in DeepDx allow it to analyze a variety of tissue types. It is available to either be installed on a single desktop workstation or be deployed on the cloud.

The prostate cancer module in DeepDx is able to recognize prostate carcinoma. This module can perform screening and highlights locations of interest using colored contours which represent different Gleason patterns.

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The Value of One

Each task – and each person – in the laboratory is vital

It's election season for this Canadian-born, postal-voting editor! And, as I write this, I've just finished casting my vote in the Canadian elections – a process that involved two slips of paper, three separate envelopes ("place your ballot in the inner envelope; place the inner envelope in the outer envelope; place the outer envelope in the return envelope"), and an extra survey just in case I want to review my voting experience. (Ask me after the results are in!)

Doesn't that seem like an awful lot of trouble to go to over a single vote? After all, there are 37 million people in Canada – how important can my single slip of paper be?

As I was mailing my ballot, I started thinking about the misconception that one voice, one person, does not matter. I see the same misconception in healthcare. It's not uncommon for one person's contribution to patient care to go unnoticed or undervalued – the patient transport assistant who brings them from point A to point B, the phlebotomist who draws blood for an important test, or the laboratory medicine professional whose job it is to perform the test and report the results. Often, the lab can seem like a "black box" and its occupants merely cogs in the testing machine.

But that is not the case. Each person's contributions to the lab are vital, from the one who delivers the specimen to the one who signs the final report. Without someone to gross and someone to annotate and someone to wipe down the bench afterward, the laboratory could not function – and patients would not receive timely and accurate diagnoses and appropriate treatments.

All too often, it's easy to forget the value of one task, or one person, in the frenetic pace of a busy laboratory. But don't undervalue yourselves or your colleagues – remember that every single person in the laboratory is a key contributor to its success.

Going back to my vote: four years ago, a Canadian election was literally won on a coin toss because two candidates received exactly the same number of votes. Before that, half a dozen others were won by a margin of less than 1 percent… I guess it was worth all that envelope-licking after all.

Michael Schubert
Editor

Upfront

Reporting on research, innovations, policies and personalities that are shaping pathology today.

Do you want to share some interesting research or an issue that will impact pathology?

Email: edit@thepathologist.com

A Clearer Picture

How does a new quality control tool filter digital slide images by quality?

Knife chatter – a term with which some pathologists will be all too familiar – refers to a compromise in the quality of glass slides caused by issues with slide preparation, such as air bubbles, smears, or ragged cuts in the tissue. Pathologists analyzing slides under a microscope can easily identify those affected by the issue – but when it comes to digital pathology imaging, knife chatter introduces a whole new standardization problem. To address it, Anant Madabhushi and Andrew Janowczyk of Case Western Reserve University's Center for Computational Imaging and Personal Diagnostics have developed a program that aims to ensure the quality of digital slide images.

As digital pathology continues to alter the landscape of clinical diagnostic workflows, more and more physicians have turned to digital imaging systems to analyze tissue. At the moment, though, there are no standards for the preparation and digitization of slides – and practically perfect ones are routinely found alongside those of poor quality. In the context of machine learning, this can mislead computer programs trying to recognize the appearance of cancerous cells.

When Janowczyk discovered that about 10 percent of the 800 cancer samples he reviewed in The Cancer Genome Atlas (TCGA) had issues, such as cracked slides or air bubbles, he decided to create an application to help. The new quality control tool, called HistoQC, prevents the need to manually review glass and digital slides, instead offering an automated approach.

HistoQC locates artifacts in slides that need to be reproduced and identifies areas unsuitable for computational analysis. The program uses a combination of image metrics, such as brightness and contrast, alongside features such as edge detectors and supervised classifiers to pinpoint the slide regions that are most accurate. Users can then monitor and filter the slides in real-time and explicitly define acceptable artifact tolerances. When two pathologists reviewed HistoQC on 450 slides from TCGA, the output was suitable for computational analysis in over 95 percent of cases (1).

Having recently secured a three-year, US$1.2 million grant from the National Cancer Institute to further develop HistoQC, Madabhushi describes the technology as a step toward the "democratization of imaging technology." The team hopes to accelerate the widespread use of AI for interrogating tissue images and, to this end, they have made HistoQC an open-source platform – freely available for all to access, modify, and extend via an online repository.

Reference

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A Pharmacogenomic Promise

New testing can improve personalized treatment – but only with judicious validation and use

Pharmacogenomic testing is an increasingly significant part of many laboratory medicine professionals' work. The more we learn about genes that affect drug efficacy, metabolism, or even the likelihood of adverse events, the more we can test to ensure that each patient receives the appropriate dose of the appropriate drug with the appropriate monitoring. However, not all tests are equal; some have a greater evidence base behind them or may simply be easier for clinicians or patients to understand. As a result, the Association for Molecular Pathology (AMP) has developed a set of best practices for clinical pharmacogenomic testing. We spoke to Jordan Laser, Medical Director of Long Island Jewish Medical Center – Pathology and Laboratory Medicine and Chair of AMP's Professional Relations Committee, to learn more.

How is the rise in pharmacogenomic testing affecting pathologists and laboratory medicine professionals?

AMP members are among the early adopters of molecular diagnostic testing in clinical settings, and we are committed to improving professional practice and patient care. Our members have accumulated substantial knowledge and expertise that is useful for laboratories performing pharmacogenomic tests, and our goal is to promote standardization of pharmacogenomic testing across clinical laboratories.

AMP continues to evaluate the evolving landscape of pharmacogenomic testing. As part of this evaluation, a group of leaders determined that clinically meaningful pharmacogenomic tests are poised to improve patient care and professional practice – provided that certain conditions are met. The set of conditions include:

- All health-related pharmacogenomic claims must have well-established clinical validity.
- The pharmacogenomic testing provider must comply with the Clinical Laboratory Improvement Amendments statute and regulations.
- The pharmacogenomic test report should be easily understood by healthcare providers and include the interpretation of the findings, the significance of the results, and the limitations of the test.
- Patients should not change their treatment plan without first talking to their healthcare provider.

What defines a clinically meaningful pharmacogenomic test?

Clinical pharmacogenomic tests are valuable tools that can help healthcare providers determine the optimal medication or treatment for a specific patient. As in all other practices of medicine, supporting clinical validity must be determined before the test is offered to patients. Evidence may be demonstrated through peer-reviewed literature, clinical practice guidelines, and/or FDA drug labels. One organization that develops clinical practice guidelines for pharmacogenomic testing is the Clinical Pharmacogenetics Implementation Consortium (CPIC). CPIC has developed a number of gene-drug practice guidelines to help determine a clinically meaningful test.

AMP encourages the use of such clinical practice guidelines. The AMP Pharmacogenetics (PGx) Working Group is also working on a series of evidence-based expert consensus opinion recommendations designed to help standardize alleles that should be included in clinical testing for frequently used genotyping assays. The Working Group started with *CYP2C19* and *CYP2C9* genotyping panels due to the widespread adoption of these tests and our desire to help physicians, pharmacists, researchers, and other stakeholders better understand what these panels include and what the test results mean.

We recognize that this is a quickly evolving field and that patients gain the most benefit from pharmacogenomic testing when healthcare providers can easily determine when a patient's genotype indicates an actionable treatment decision. For this reason, AMP supports test reports that include the metabolizer status based on the genotype for the genes that affect drug metabolism; a list of the drugs for which responsiveness may be affected by the genotype; a generalized statement to alert healthcare providers when alternate dosage or drug treatment may be considered based on the results; and a list of resources and references that healthcare providers can use to learn more about the genotyping results.

What advice do you have on playing an active role in this testing?

We're just beginning to realize the full potential of clinical pharmacogenomics in the era of precision medicine. These groundbreaking tests provide substantial benefits to patients when the drug-gene association is supported by strong scientific evidence and the healthcare provider is easily able to determine the actionable prescribing decision. Our new position statement on pharmacogenomic testing leverages our community's collective expertise in this rapidly developing field and reflects AMP's ongoing commitment to improving professional practice and patient care.

Unraveling Complexity

A new deep learning model may yield novel associations between genes and diseases

If there's one thing we are learning from our ever-increasing fount of genetic knowledge, it's that the relationships between genes and diseases are often complex. The more mutations we find and the more genes we associate with particular diseases, the more tangled the web appears. But with thousands of biomarkers available to us and new ones discovered all the time, how do we determine which are truly causative, which associated, and which merely coincidence?

A team of researchers from King Abdullah University of Science and Technology is harnessing the power of artificial intelligence to do just that, with a new deep learning model that the researchers say outperforms existing methods. They call their approach GCN-MF: graph convolutional networks and matrix factorization (1).

A graph convolutional network is a deep learning model that, in this case, analyzes how genes network and the similarities among genetic diseases. The resulting data is then organized into matrices that yield further information on gene–disease associations. Unlike existing methods, which are based on linear models, GCN-MF can examine nonlinear associations to yield brand-new information about the genes involved in complex diseases.

"By making use of more information, we achieved better accuracy than the state-of-the-art methods currently in use," first author Peng Han said in a recent press release (2). He cautions, though, that the model isn't yet ready for prime time. First, he and his colleagues need to incorporate new types of data and challenge it with new types of problems – and then, hopefully, GCN-MF can make its debut in the clinic.

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A Renal Revolution

Artificial intelligence is making a name for itself on the kidney biopsy scene

Kidney disease diagnosis is not always easy – renal pathology is an uncommon specialty and reading kidney biopsies can present a challenge. But what if computational pathology could help improve the diagnostic process and the accuracy of the ultimate diagnosis?

Two recent studies have taken on the task of building a better mousetrap by creating computational tools to tackle areas of difficulty in kidney disease diagnosis.

The first study, performed by researchers at the University at Buffalo, combined image analysis and machine learning into a digital algorithm to classify renal biopsies from patients with diabetic nephropathy. Although glomerular structure is complex and can be difficult for even human pathologists to fully quantify, the researchers provided a set of simplified components for the algorithm to use in its classification. Ultimately, the digital classifications of biopsies from 54 diabetic nephropathy patients substantially agreed with those of three different human pathologists – and the algorithm was able to detect "glomerular boundaries […] with 0.93±0.04 balanced accuracy, glomerular nuclei with 0.94 sensitivity and 0.93 specificity, and glomerular structural components with 0.95 sensitivity and 0.99 specificity (1)."

The second study, conducted at Radboud University Medical Center, used a convolutional neural network to extend the analysis to multiple tissue classes in kidney transplant biopsies – an area where work is already time-consuming and unreliable (2). The network's performance varied depending on the tissue type; glomeruli were a particular strength, with the network detecting 92.7 percent of all glomeruli and exhibiting a 10.4 percent false positive rate (3). Although there remains room for improvement, this first convolutional neural network of its type heralds future possibilities for deep learning and neural networks in the day-to-day diagnostic workflow.

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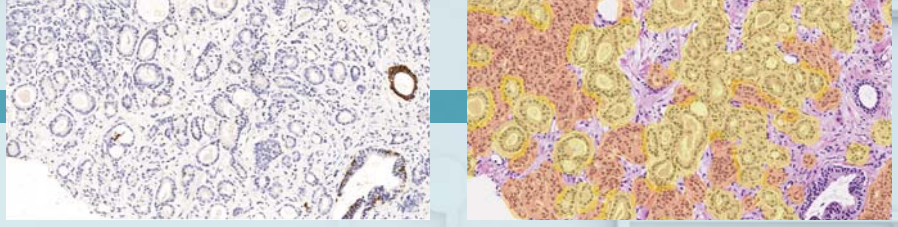

Deep Bio's DeepDx-Prostate tool in action, highlighting different tissue areas for Gleason scoring; pattern 3 in yellow, 4 in orange.

Deep Bio's Deep Dive

Precision cancer diagnostics for all

Our understanding of disease and the agents that cause it is exploding. More than ever, we can examine a patient's genes, blood, environment, family history, and personal circumstances to identify and monitor potential problems. But although it's vital to know as much as possible about a patient's health, the sheer volume of data poses a challenge in diagnosing disease and selecting the best possible treatments. Add to this the growing shortage of pathologists and it's clear that a new approach is needed.

This is particularly true in prostate cancer – a field that has often faced controversy over the "best" way to detect and characterize the disease. Does the biopsy show cancer? If so, what type and at what stage? Which is the best option for treatment? Answering these questions can be difficult, time-consuming, and controversial – but, with the advent of artificial intelligence (AI) diagnostics, there is a light at the end of the tunnel.

The AI advantage

Deep Bio, a company dedicated to improving diagnostic processes and expanding access to quality healthcare, sees AI as the way forward. Their goal? To make medical diagnoses more reliable and reproducible, while reducing turnaround times and easing the burden on pathologists and laboratories worldwide. That's why they've chosen to make their first target prostate cancer – a disease of many challenges.

The company's first solution is DeepDx-Prostate, a system that uses a trained deep learning model to spot acinar adenocarcinoma of the prostate on scanned hematoxylin and eosin slides. The tool's basic function is to identify slides that show evidence of cancer, allowing pathologists to concentrate their attention on these cases – a streamlining effort that allows more cases to be processed in less time, reduces the overall workload of pathologists, and alleviates the mental and physical fatigue of long hours spent hunched over a standard microscope.

But the AI doesn't stop there; it can offer even more detailed information. How? By using Gleason scoring, the system can identify areas of interest, highlight tissue regions with different colors, and provide results including:

- Gleason score
- relative proportions of each Gleason pattern
- percentage involvement of cancer
- representative lesion images taken from the slide

It can even generate pre-filled pathology reports containing the score and representative images to save even more time and effort.

Knowing the score

Gleason scoring can be tricky. DeepDx-Prostate can help by providing not only automatic scoring, but also a breakdown of how that scoring was achieved, complete with images. Different colors highlight areas with features representative of different Gleason scores, allowing pathologists to take a birds'-eye view of a case and make quick decisions. Company founder and CEO Sunwoo Kim said, "Pathology reporting guidelines have recommended to particularly include the percentage of Gleason pattern 4, as it provides clinically significant information on predicting patients' prognosis (1)." Currently, the model is expected to achieve a similar level of agreement to human pathologists – and, with more data, it's designed to become even more accurate (2).

For consensus annotation of complicated cases, the DeepDx-Prostate model can be deployed with all of the functionalities of the local tools – but on the Internet, so that pathologists can share, annotate, and discuss slides with colleagues. The system is in preparation for an open beta trial next year as DeepDx Connect - Prostate. Together, these tools support pathologists in the laboratory and help them move toward Deep Bio's ultimate goal – to make high-quality pathology portable and accessible to all.

"Currently, the model is expected to achieve a similar level of agreement to human pathologists – and, with more data, it's designed to become even more accurate."

DeepDx Connect - Prostate is registered as in vitro diagnostic in compliance with the CE. MFDS Korea approval is in progress. US market entry is expected to begin in 2020.

For Research Use Only. Not for use in diagnostic procedures.

For more information, contact sales@deepbio.co.kr

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1. *Biospectator (2018). Available at: https://bit.ly/2pDSelP. Accessed October 3, 2019.*
2. *H Chang et al. Poster presented at USCAP 2019; March 16–21, 2019; National Harbor, USA. Abstract #811.*

In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of laboratory medicine. They can be up to 600 words in length and written in the first person.

Contact the editors at edit@thepathologist.com

Worth Fighting For

It can be a struggle to make the business case for digital pathology – but the rewards are great

By Peter Carey, Consultant Hematologist and Clinical Lead (North of England Haematological Oncology Diagnostic Service), Royal Victoria Infirmary, Newcastle upon Tyne, UK

When it comes to digitization, pathologists are late to the party.

A decade or two ago, radiologists realized that they could get rid of their nasty chemicals and heavy, expensive, silver-laden films (which had to go into great big packets for preservation, be carted around the hospital, and be put on lightboxes for MDTs). For them, digitization seemed the obvious solution. Of course, there was a bit of resistance at first from people who worried about the quality of the images – but now, with modern monitors, it's clear that isn't a problem. But radiology had one major advantage over pathology: they save a lot of money by doing digital work instead of chemical use, film production, and physical storage. Pathology's digitization is not instead of; it's as well as, because we still have to make slides, stain them, scan them, and usually keep them for medico-legal reasons even after creating a digital version.

There are, of course, huge advantages in terms of workload distribution and archive accessibility – no more digging through a room full of glass slides to find a single image – as well as enabling use to apply artificial intelligence software. Unfortunately, in our case, we're not saving anything; we're paying for these advantages. And that's particularly difficult in the resource-challenged environment we all live in at the moment. There's not enough money in healthcare to do everything patients need, and the laboratory often ends up last in the queue. If there's something we truly need, we have to fight for it.

Is it worth fighting for? I think so. In the North of England, where I work, we have a shortage of medical hematologists and specialist biomedical scientists to cover out-of-hours provision of morphological expertise with compliant sustainable on-call rotas – particularly in the region's more remote hospitals. For example, a biomedical scientist from biochemistry in one of those locations might need support at two o'clock in the morning, faced with the prospect of looking at a blood film they don't fully understand. Can we help out? Until now, we've solved that problem either by expecting the local hematologist to come into the lab in the middle of the night and look at the slide or by putting the slide into an urgent taxi to one of the larger institutions. These options become less sustainable in the light of rota requirements, recruitment problems, locum availability, and the cost of locum cover. But the provision of a robust diagnostic hematology service is critical for the operation of any hospital providing a 24-hour acute service. Suddenly, you have a problem that interests administrators – and a potential argument for resourcing an alternative. We have been able to obtain pilot funding for scanners on the basis of out-of-hours blood film reporting (and using the opportunity to explore daytime use as well); others may have different reasons. It's a matter of finding a problem that people are prepared to throw some money at!

Some time ago, I met a Californian

couple who had originally come to England for a year's sabbatical to accommodate the wife's career as an academic historian. The husband, a senior radiologist, had taken the year off work – but, when the move became permanent, he needed to find a job. It turned out that his hospital in California was struggling to get radiologists to report cross-sectional imaging on patients at night. Thanks to digitization, he was employed full-time during his day to report overnight scans eight time zones away. One day, I hope the same will be possible for pathologists and laboratory medicine professionals worldwide.

Routine Diagnosis: 100 Percent Digital

Fully digitizing anatomic pathology results in greater staff satisfaction and lab efficiency – but is also a pre-requisite for computational pathology

By Juan Antonio Retamero, Pathologist at Granada University Hospitals, Granada, Spain

Granada University Hospitals, a group of two teaching and two district general hospitals integrated into the Spanish public healthcare system, have been using digital pathology for primary diagnosis of all histopathology specimens since September 2016. Since its implementation, approximately 160,000 specimens have been digitally diagnosed – around 800,000 digitized glass slides, including routine hematoxylin-eosin, special stains, and immunohistochemistry samples. Microscopes have been largely replaced by computer screens, and all our digital histology images, stored in local servers, are instantaneously available to our staff across the four hospitals.

The creation of a fully digital multi-site network has brought about several advantages, most important of which is the ability to assign caseloads according to specialty interest among our pathologists, regardless of their location. Pathologists at the peripheral hospitals can request immediate consultations from specialists located at the central hospital in Granada. Sharing cases with colleagues and requesting "curbside consultations" is straightforward, even between distant sites.

Pathologists were attracted to digital diagnosis from the start. The excellent image quality, particularly at low power; the availability of digital tools for marking, counting mitoses, and measuring lesions and their distance to surgical margins; the orderly disposition and immediate availability of digital images, including archived images; and the added ease of preparing for multidisciplinary team meetings and teaching sessions – all of these advantages made our pathologists keen to transition to digital diagnosis. Together with the rational case allocation permitted by the creation of a fully digital multi-site network, these factors have resulted in a more pleasant and productive working environment. Once our pathologists tried digital, they never looked back.

For us, digitization has paid off in many ways, from greater pathologist and lab staff satisfaction to a measurable productivity increase. Full digitization means that some lab tasks, such as slide sorting and case assembly and distribution, are now redundant. There is no shifting of glass slides across sites. For this reason, whereas some prefer a "hybrid" mode of diagnosis during the transition period (1), we decided to opt for full digitization shortly after rollout.

"Once our pathologists tried digital, they never looked back."

The adoption of digital pathology has resulted in improved efficiency. Like many public healthcare settings, our labs have experienced annual caseload increases ranging from 5 to 9 percent per annum. In addition, we have experienced staff vacancies due to non-replaced retirements. This has translated to an increase in the number of cases signed out per pathologist each year following digital implementation. The total number of cases that each pathologist signed out per year since going digital has increased, on average, 21 percent after adopting digital pathology (2).

Despite the immaterial benefits of working with digital tools in a glassless and more ergonomic environment, the investment required to implement digital pathology can only be justified if the cost incurred is outweighed by the benefits obtained. A cost-benefit model (3) proposes that improvements in productivity of at least 10 to 15 percent are required to amortize the investment

after one to two years. Following this model, the fact that we were able to absorb a 21 percent increase in cases per pathologist suggests that amortization occurred even faster. In any case, the savings incurred by doing more work with fewer pathologists in the three years since the implementation of digital pathology justifies the investment from a pecuniary point of view – but it is equally important to remember that computational pathology, the so-referred third revolution in pathology (4), can only take place in digital labs.

Juan Antonio Retamero is a consultant for Philips Digital and Computational Pathology.

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Precisely What You've Been Looking For

Image search plays a key role in getting useful information out of digital data

By Patrick Myles, Chief Executive Officer at Huron Digital Pathology, St. Jacobs, Canada

According to a study from the Massachusetts Institute of Technology, 90 percent of information transmitted to the human brain is visual and we can identify images we see for as little as 13 milliseconds (1). No other profession understands this more intuitively or puts it into practice more than pathologists. Yet even as progressive hospitals adopt digital workflows in pathology, we are hobbling along with text-based search to find the data we need. What if we could search visually based on the content of the image? How much would we improve the quality and speed of diagnosis? How much could we accelerate discovery?

Imagine, for example, that a pathologist is reviewing a difficult case. What if they could instantly search and retrieve multiple results of similar-looking tissue along with the associated pathology reports from trusted colleagues? They could locate information from others at their hospital or hospital network, or even from experts around the world. How much could that help inform their diagnosis? And the benefits aren't limited to the clinic. Researchers could use image search to discover previously unknown connections between cancer subtypes – or, if we think big, throughout the entire genome.

At the Pathology Visions conference in Orlando in October, Hamid Tizhoosh from the Kimia Lab at the University of Waterloo reported on a recent validation of image search, in which we indexed ~30,000 whole slides from 11,000 patients (2). The search encompassed 25 organs and 33 cancer subtypes from the NIH/NCI public dataset (3). From the project, we learned that it is possible to build diagnostic consensus with high confidence. The search engine itself uses a "majority vote" system by which it compares new, undiagnosed cases against all existing diagnosed cases in its dataset – a system with great success. In frozen sections and diagnostic slides, accuracy for certain cancer types approached 100 percent. We identified a positive correlation of 80 percent between the number of patients and the accuracy of majority consensus – that is, the more data the better.

Over the next five years, hospitals and labs will produce hundreds of millions of digital slides, exabytes of unstructured image data, and tens of millions of pathology reports. Image search will become the "must-have" functionality to bring intelligence to the huge quantity of unstructured image data, with the far-reaching potential to connect pathologists to the collective knowledge of their colleagues. Keep your eye on this technology – because, without it, we risk simply bypassing huge amounts of valuable information.

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The Future of Pathology Informatics

In today's digital era, the laboratory can be the architect of change

By E. Blair Holladay, CEO of the American Society for Clinical Pathology, Chicago, USA

In September, we lost a giant in medicine and medical research: Donald A.B. Lindberg. As Head of the National Library of Medicine, Lindberg modernized and digitized the vast amounts of materials the library housed and changed the way medical information is shared across the world. Lindberg was also a pathologist and a leader in medical informatics, using data and technology to deliver better patient care and information for improved outcomes. What he started decades ago has helped shape what we know today as pathology informatics.

Pathology informatics is an evolving field – and one that is primed to disrupt health care as we know it. In today's patient-centric healthcare environment, patient data offers a wealth of opportunity. Being able to see the whole patient record is critical to better understanding a patient's diagnosis and developing a more personalized treatment plan. There is so much we can learn from one person – but, with the information that we get from a collective of patients, we can learn an order of magnitude more.

And that's where informatics comes in. Connecting data to parse solutions to diagnostic issues is driving modern pathology practice. Rather than let data sit in a black hole, pathology and laboratory professionals need to be the leaders who bring it to light, shaping the information held within into something more useful for clinicians and patients alike.

Over the past decade, pathology informatics has made – and continues to make – great strides. And, without a doubt, pathology informatics will fuel personalized medicine. It will push the boundaries of what we can do, and its potential is almost limitless. It is the foundation upon which the future of healthcare will be built.

But we're not there yet.

There is still a need for faster, better information exchange across different systems (while still complying with patient privacy). Once we have the data, we need the programs and the technology for meaningful interpretation. And, as we use data for more personalized diagnoses and treatment plans, insurance companies need to understand how best to execute their reimbursement processes.

Since the dawn of modern pathology, we have been the providers of laboratory data and clinicians have been interpreters.

"Pathology informatics is an evolving field – and one that is primed to disrupt health care as we know it."

But that can't happen in today's environment, where value-based health care is becoming the norm. The scope of the data we receive via informatics pathways is huge and, to be effective, it must be broken down into insightful information. And we – pathologists and laboratory medicine professionals – are the change agents who can take the data from idea into integration.

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Empowering Precision Diagnosis Through Digital Pathology

Digital pathology is the way to the lab of the future – and the way to superior patient care

As digitization continues to sweep the diagnostic arena, pathologists are increasingly using digital solutions instead of microscopes to review slides and cases. Why? Because the technology offers easy access to images, simplifies external consultations, reduces the need for physical storage and transport of slides, and holds promise for a computer-assisted future. But although the benefits of digital pathology are clear, not everyone has leapt in with both feet, often citing the slow speed of slide scanning or the differences between microscope and slide images. To win over those with any doubts, digital pathology must offer a seamless, efficient user experience.

Making the leap

Digitization is becoming more affordable and accessible than ever, but whether your laboratory is low- or high-volume, you may still face obstacles to your transition to digital pathology. For instance, you may wonder whether it truly adds workflow efficiency – after all, digitization adds a step to the process of preparing slides for diagnosis.

Enter the VENTANA DP 200 slide scanner, which tackles that issue head-on with its ability to rapidly scan slides. Its dynamic focus technology can track tissue depth in real time to achieve high image resolution and it uses color management to ensure that scanned images closely match what pathologists see under the microscope. Dr. Joachim Schmid, Vice President of Research and Development at Roche Tissue Diagnostics, is particularly proud of the scanner's built-in calibration and color management.

"Together, they ensure that the output shows a very high level of consistency and quality," he says. "Everyone likes the simplicity – and when I ask users to open the images they've just scanned, it's rewarding to see their surprise at how good the images look."

Another barrier to the adoption of digital pathology may be the handling of errors and artifacts introduced during the slide preparation and scanning process. "It is quite challenging to reliably produce an image that accurately replicates what the pathologist sees in the microscope," says Michael Rivers, Vice President, Digital Pathology, Roche Tissue Diagnostics.

Schmid agrees: "Scanners in the past were sensitive to variations in slide dimensions and preparation artifacts. The VENTANA DP 200 uses a slide tray to move slides around and can be run with a no-touch interface, meaning the user can load slides and the system will automatically scan them."

By minimizing physical contact with the slides, the scanner helps to eliminate errors and slide damage. "The aspect of the VENTANA DP 200 that I appreciate the most is the simplicity of the design, with one moving part during scanning, which leads to robust operation and reliable performance," says Rivers.

Case management software is another concern for some laboratory managers considering a move to digital – there are seemingly endless options, each with its own set of pros and cons. Dr. Eric Walk, Chief Medical and Scientific Officer at Roche Tissue Diagnostics, says, "As a pathologist, I'm really drawn to the 'case view' functionality in the Roche uPath enterprise software. The ability to view a digital tray of slides and seamlessly zoom into any one of them to conduct diagnostic analysis is a game-changer in my opinion."

It should come as no surprise that smart software is key to an efficient workflow. "The VENTANA DP 200 uploads images immediately to uPath software and makes it easy to access slides within the software environment," says Schmid. "By automatically identifying the barcodes on the slide and getting information from the LIS to sort the slides into cases, a pathologist is able to start working on a case right away."

Rivers concurs: "The ability to scan high-resolution whole-slide images and present them in a viewer that supports the pathologist's workflow brings a new level of speed and efficiency to anatomic pathology."

Such ease of access plays to one of digital pathology's major strengths: the ability to view cases regardless of one's location for a variety of applications.

"The digitization of anatomic histopathology enables a completely new diagnostic ecosystem that ultimately leads to better patient care," says Walk. "Whether through faster, telepathology-driven second opinion consultations, novel pathologist education and training programs, or even crowdsourcing approaches, this technology is having a transformative effect on the

Having a system that allows the user to be as efficient as they can be with the microscope is critical for the success of digital pathology.

practice of pathology."

There is tremendous potential value in the use cases made possible through digital pathology that go beyond routine scanning. Digital pathology can enhance workflows for frozen sections, tumor boards, and even education.

"Making the review independent from the location of the slide allows for very different ways of practicing pathology," says Schmid. "It makes it easy to access expert pathologists anywhere in the world and improves the quality of diagnosis."

A longtime player in the digital pathology space, Roche is laying a new foundation with the launch of the VENTANA DP 200 and uPath software. The goal? To make digital pathology simple and reliable for pathologists and laboratory medicine professionals. Not all labs are able to go fully digital at once. It's important for labs to have digital pathology partners that allow them to gradually scale to full digitization – and to offer improved quality assurance, speed, and diagnostic accuracy.

A digital future

The digital transformation is revolutionizing every industry – and pathology is no exception. "We're rapidly entering a new era in which pathologists are adopting a new mindset and acceptance of digital and artificial intelligence (AI)-based assistance," says Walk.

As workloads continue to increase and precision interpretation of complex biomarkers becomes increasingly essential, Schmid predicts that digital pathology will become the standard in pathology practice and replace the microscope as the pathologist's main tool.

"A key for the digital transformation will be to create a seamless experience for the user – from the lab to the slide review to the analysis of images. Having a system that allows the user to be as efficient as they can be with the microscope is critical for the success of digital pathology."

Walk cites the VENTANA DP 200 in combination with uPath software as an excellent example of meeting this need. Rivers adds, "I think we now have solutions that provide real value in terms of both workflow efficiency and new medical insights. In the near future, we will see image analysis moved into routine use in clinical pathology. Roche is leading the way in developing new analysis tools to enable more consistent results and more diagnostic confidence for pathologists."

In short, digital pathology is more than just a buzzword. It has the power to transform pathology in two key areas – workflow and medical value – which ultimately results in better patient care.

"On the workflow side, telepathology allows ready access to cases even when the pathologist is geographically separated from the histology laboratory," says Walk. "On the medical value side, image analysis algorithms and telepathology consulting support more accurate diagnoses."

A pathologist's work starts with a great image and ends with the best possible standard of care for patients – and that's what Roche Digital Pathology strives to support.

https://go.roche.com/digitalpathology

Erasing Pathology's Borders

HOW EVEN THE SIMPLEST OUTREACH CAN CHANGE THE LIVES OF PATHOLOGISTS AND PATIENTS WITH LIMITED RESOURCES

When you picture a pathology lab, what do you see? Perhaps you're imagining stations for processing and preparing tissue samples, or racks of tubes containing blood to be examined, or even – in particularly advanced scenarios – a bank of computers with high-resolution monitors for viewing digital slides.

Although these are all standard sights in many laboratories, many pathologists and lab medicine professionals are not so lucky. For many of them, even simple staining facilities are a distant dream – and those who work in the most resource-limited settings are often desperate for assistance. That's why, increasingly, these pathologists and laboratory staff are turning to digital pathology in its most basic sense.

They may use low-end smartphones to snap photographs of gross pathology or rely on DIY camera mounts to balance those phones on top of whatever microscope they're lucky enough to have. They may fund their laboratories out of their own pockets when the allocated money runs out. They may post photos to social media to ask for expert consults because there are simply no specialist pathologists in their area. It's a different world to the shiny new technologies many laboratory medicine professionals are familiar with – but people like Olaleke Folaranmi, Peter Carey, and Yuchun Ding are seeking to bridge the gap between the two worlds.

A FRIEND TO ALL PATHOLOGISTS

Yuchun Ding and his organization – X-WOW! – strive to open doors for pathologists worldwide

Michael Schubert interviews Yuchun Ding

TELL US A LITTLE BIT ABOUT YOURSELF...

I am an ordinary postdoctoral computer scientist. Since 2013, I have worked on whole-slide digital pathology image analysis using artificial intelligence (AI). One day, I asked myself, "Have I done something that has made a real difference in healthcare? How many lives have I saved? How many pathologists have I helped?" I was ashamed to admit to myself that the answer was zero.

My status as "a computer scientist with no experience in biology" was not helping me to change the answer to that question, so I decided to take a big step back and spend a little while observing what pathologists actually do. I have now been to the mortuary to watch a close-up autopsy at seven o'clock in the morning. I have been a "fly on the wall" observing the pathology workflow. I have even bought my own microscopes and staining kit to replicate at home what I've seen done in the lab. I'm not sure I would recommend this to other computer scientists, but I pricked my own fingers, stained the blood, and looked at it under the microscope to help me think about developing software from a pathologist's point of view.

I've also done some unusual experiments such as staining colostrum (breast milk) after my second son was born and staining the red juice from medium-rare steak to find out what exactly is in it, you can also find them on my twitter page, and more.

WHAT EXACTLY IS X-WOW!?

Posting fun experiments on Twitter was only my first step. It helped me to understand what pathology is about; who the "celebrities" in the field are; and the differences between monocular, binocular, and trinocular microscopes. I also discovered that microscopes are expensive to buy and that not many people can afford them, especially in resource-limited settings.

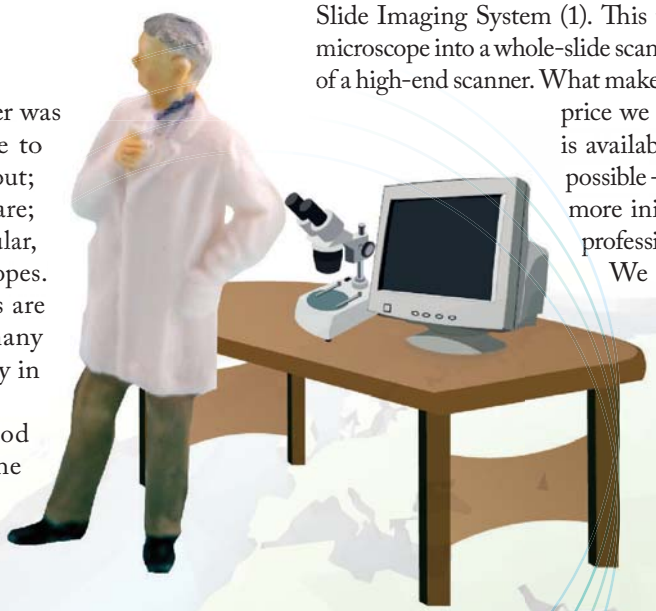
Sharing is what makes a good pathologist. Being active in the pathology community for few months doesn't turn me into a pathologist, but I can still share in a different way. A few days after my wife and I created X-WOW!, an organization with the goal of "making microscopes easier to access," a microbiology student at a Nigerian university got in touch.

He said, "I am optimistic about a bright future by building a career in microbiology, but one must agree that it takes both hard work and learning with the right tools and equipment to gain full expert knowledge. At secondary school, while learning the basic concepts of microbiology (viruses, bacteria, fungi, and so on), I never got a chance to use a microscope (either compound or electron) – one of the most important tools for studying microorganisms.

"The study of microorganisms requires that we students conduct experiments using the microscope, discuss with one another, and get practically involved with our hands and eyes – but instead, we remained passive participants, expected only to listen, but not to see things for ourselves. The inadequacy or total lack of equipment and instruments here decreases students' participation in science, and particularly microbiology. Having an awareness of African schools' deficiencies and how they act as a setback to students' involvement in microbiology, and wanting to create a solution to that problem, I am readily available to assist and also gain from this." His comments basically mirrored the reasons my wife and I started the organization – and the main reason we named our (free) virtual microscopes after him. We want to help him achieve his dream of microbiology for all in Africa.

Because we are in the early stages of X-WOW!, we have thus far used our own savings and whatever donations we have received to make microscopes available to people who can bring ideas into reality. Although we are truly grateful to those who have supported us in the past, we know we shouldn't ask for more from them; that's why, after six months of hard work, we have now released our own commercial X-WOW! Manual Whole Slide Imaging System (1). This tiny device turns an ordinary microscope into a whole-slide scanner at one-twentieth of the cost of a high-end scanner. What makes it unique? We offer the lowest price we can, so that digital pathology is available to as many pathologists as possible – and we use the profits to fund more initiatives to support laboratory professionals in deprived areas.

We would also love to receive sponsorships to keep the work going long-term. We once received a donation from an entrepreneur who wanted to see his money bring to life projects in cancer diagnosis



using digital technology. We believe there are more people out there who share the same dream, and we hope to connect with them to make it a reality.

WHAT HAS X-WOW! ACHIEVED SO FAR?

Since December 2018, we have donated seven microscopes, including one converted to a whole-slide scanner. Let me tell you some of my favorite experiences.

First, I've always wanted to be a Santa, ever since I was a child. I don't have a white beard (yet), but luckily, I do have a big belly. In December of 2018, one week after X-WOW! was born and two weeks before Christmas, I posted a tweet to give away a microscope. I wanted to make a child's dream come true and, hopefully, to inspire a future pathologist. I even included some educational animal histology slides!

The event went really well and, two days later, we gave the microscope to a boy named Josh. This was actually a perfect choice, because his mother is a school biology teacher who can assist him in using the microscope properly. They even did an entire school project on hunting for tardigrades (water bears)!

The outcome of that first initiative encouraged me to keep it going. One day at work, I met a hematological pathologist who was providing remote consultation to a pediatric oncology unit in Malawi through microscopic images. However, half of the cases they sent were non-diagnostic; the image quality was poor and the fields of view were tiny. Whole-slide imaging was a perfect solution, so I decided to upgrade their imaging system with a manual whole-slide scanning system from a commercial partner. It cost so much less than an automated machine (under £5,000) – but, of course, even that was totally beyond the means of a small lab in Malawi, so I launched a fundraiser to buy the entire system.

Time was tight, because the British oncology team was planning to visit Malawi very soon; in the end, we bought the system before reaching our fundraising goal so that we could make sure they had it in time. Fortunately, a week later, we received a full donation and our story "hit the big time." It featured on the news (2) and we were invited to write about our work for the July 2019 issue of the Royal College of Pathologists' bulletin.

After the successful story in Malawi, I organized a pop quiz competition on Twitter as a little celebration and printed a lymph node T-shirt for a prize draw. The lucky winner was Tania, a Spanish pathologist. She loves it!

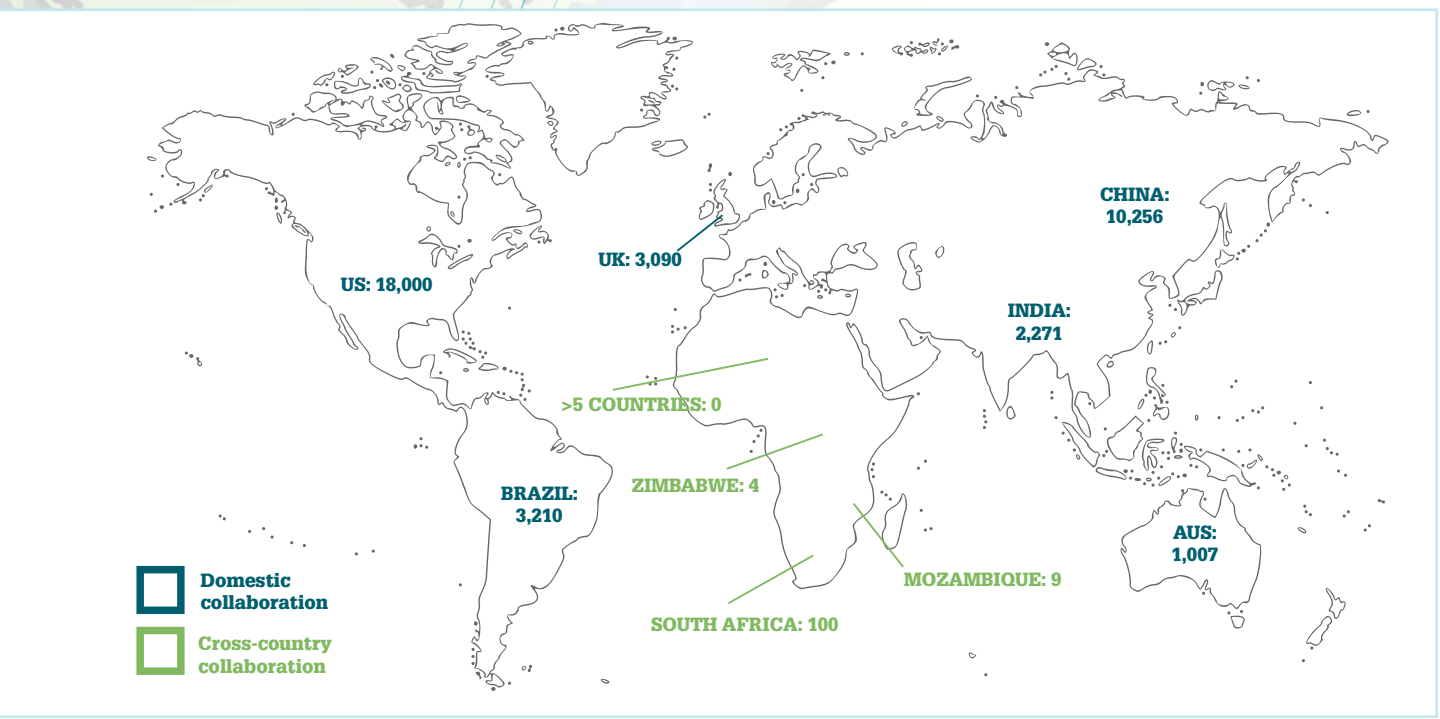
We also asked Finelia, a young cancer patient from Malawi, to paint a picture of her dream job. Her response? "I wish to become a police officer." We took her dream back to the UK with us and used it to help explain our story and to spread awareness of the cancer diagnosis service available in deprived areas.

Another one of our proudest moments was supporting Olaleke Folaranmi, a kindhearted Nigerian pathologist, to thank him for sharing great content on Twitter and to help him encourage African medical students to choose pathology as career.

HOW DID THAT COME ABOUT?

One day someone retweeted a post from Olaleke's story. In it, he said, "I sacrificed everything possible to be here… that meant getting great quality images for #Pathology friends, colleagues & experts to view/comment on. All these were achieved at great personal costs: loans for microscope camera, mobile phone, PC, and expensive data subscription."

I thought, isn't that the greatest example of a good pathologist? That's why I immediately decided I was going to help him. I had a chat with him privately and what triggered me most is when he said, "It is difficult to be different in this country. Most of my colleagues are leaving the country because



Numbers of pathologists suitable for collaboration.

of frustration. But I believe I can change pathology here in the future, and I can always use a personal microscope to encourage those close to my workplace (medical students) to decide on pathology as a career."

It's very rare to meet people like Olaleke and he deserved a present! I wanted to use the momentum generated by his story to encourage more people like him. Timing is important, so I ordered the microscope first thing in the morning and had it sent by express delivery so that it arrived less than two weeks later. I also setup a fundraising page to invite people to contribute to thank him for his great work – and we've managed to raise £120 so far!

WHAT WOULD YOU LIKE TO ACHIEVE NEXT?

Digital pathology has a reputation for being exclusively for the "big, rich laboratories." There are hundreds of thousands of labs around the world that need digital pathology to receive second opinions remotely and rapidly, but most of them can't afford expensive machines that cost six figures. I'm currently working on an ambitious project to help the Caribbean islands go digital (3). One of the pathologists there told me, "It seems as though the small labs like us have been forgotten by those big companies."

Ultimately, X-WOW! is trying to establish an inclusive ecosystem for pathology. The dream is that pathologists from anywhere around the world can learn and make diagnostic decisions as a group digitally, remotely, and rapidly to minimize malpractice. As a start, we can help small labs achieve whole-slide imaging at one-twentieth of the full cost, and we are prototyping a simplified lab information system (x-wow.org) that will be freely available to help pathologists in resource-limited areas submit, review, and share cases seamlessly across labs. It's still in the early stages, but we would welcome any feedback that helps us improve.

Achieving such an ambitious dream requires us to obtain resources and financial support for system hardening, data security, and regulatory framework enrichment. In May, we approached a number of investors to seek sponsorship; unfortunately, they were more interested in seeing how we can make a profit before they help us. That's understandable, of course, but it's not really our focus at the moment!

WHAT DIFFERENCE CAN DIGITAL PATHOLOGY MAKE IN DEVELOPING COUNTRIES?

It's a tricky question to answer. In most developed countries, the funds are sufficient, but strict healthcare regulations often delay the transition to digital pathology. In developing countries, on the other hand, the regulations are less strict – which means that, with enough sponsorship and training, labs can theoretically go digital rapidly at a large scale, making cross-country and international collaboration for remote diagnosis much quicker and simpler. Digital pathology would bridge the gap between independent labs; they could stop sending boxes of slides to the larger labs through parcel post for second opinions and people could start to sign out regardless of their location.

However, the unfortunate reality is that some of these countries have more than just a staff shortage. Some have no pathologists at all to look after a population of millions. Others have pathologists, but their labs have no internet access, digital storage, or computational power to transfer the digital slides – and even in those that do, power shortages are frequent occurrences. Some labs don't even have the facilities to perform proper H&E staining. At Olaleke Folaranmi's lab, for instance, their tissue processor stopped working. They have no funds to repair or replace it, and therefore no immunohistochemical staining, let alone digital pathology.

Recently, we realized that there are countless old or unwanted microscopes hidden in laboratory corners – often in perfect working condition, yet forced into "retirement" because the owners use other tools. That prompted us to start the Retired Microscopes Back to School Scheme (4). Our scheme helps place these microscopes in schools in deprived countries, so that those who believe they can change the world can have the opportunity to try. Our first donation, from Aleksandra Żuraw, is currently seeking a new home!

Pathologists, microbiologists, and even students who are seeking equipment, or who are finding a new home for their older devices, can get in touch with X-WOW! through our website (x-wow.com), our Twitter account (@X_WowCom), or by emailing us directly at admin@x-wow.com. It's my hope that, in the future, we'll be seen as a friendly neighborhood organization that pathologists in any situation can contact for assistance!

As well as creating X-WOW!, Yuchun Ding works as a post-doctoral computer scientist at the Interdisciplinary Computing and Complex BioSystems (ICOS) research group, and as a cancer bioinformatician at Newcastle Molecular Pathology Node (NMPN), Newcastle University, UK.

Acknowledgments: We thank all 35 people who have kindly donated to help us turn dreams into reality (5).

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FROM NIGERIA WITH LOVE

How technology and digital pathology can change the face of laboratory medicine in resource-poor areas

Michael Schubert interviews Olaleke Folaranmi

TELL US A LITTLE ABOUT YOURSELF...

I am a senior anatomic pathology resident in Nigeria. I am currently in my sixth year and hope to conclude my training before the end of the year. I have always been in love with the microscope – ever since my exposure during my first degree in microbiology. I took a liking to pathology in my fourth year of medical school. The lecturers were serious-minded; they were always punctual and well-dressed; and they taught with an aura of authority. I am a naturally curious person, so pathology was appealing to me because it offers the detailed information that is necessary to manage patients appropriately.

WHERE DO YOU PRACTICE PATHOLOGY?

I train and practice in a tertiary-level hospital in Nigeria. The facilities are quite basic and noticeably lacking in modern equipment. Economic recession and the poor funding of healthcare over the years have taken a toll! My colleagues and I are primarily general pathologists and trainees; there are no provisions for specialist fellowships in the country because of the low overall number of pathologists. Our department offers services to all the medical and surgical specialties in the hospital, and we also take referrals from private health institutions in the city. Unfortunately, we are sometimes weighed down by our inability to make definitive diagnoses due to a lack of infrastructure for ancillary testing, such as IHC and molecular studies.

My presence on social media (you can find me on Twitter at @DrGeeONE) was borne out of the need to learn from specialists in well-developed countries – masters in their fields who can offer opinions on difficult cases and provide guidance. I also encourage younger colleagues and my own peers to consider investing time into broadening their knowledge through social media.

Some of the cases I have shared in the past may have educated many (mostly younger) colleagues, particularly those that feature diseases exclusive to the tropics. For example, a few weeks ago, I shared a case of typhoid ileitis. I never imagined that many of my international colleagues would never have seen such a case before – a disease that is rampant in our part of the world due to poor sanitary conditions imposed by poverty. The feedback from this case was very encouraging and I hope to share many more of the unique challenges my country faces.

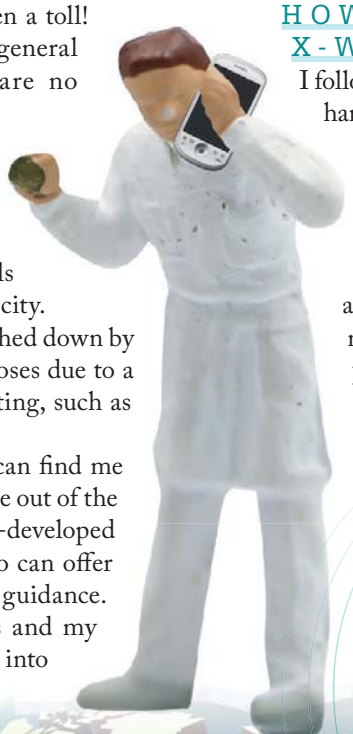
HOW DOES DIGITAL PATHOLOGY AFFECT YOUR WORK?

Digital pathology in my present context means the sharing of digital images (using phone or microscope cameras) to showcase classical pathology cases or seek informal consults via social media. There was no such thing in my department when I started residency; back then, I took pictures of difficult cases with my phone so I could view the pictures while studying at home to try to "picture match" with photographs on pathology atlases. I stumbled upon pathologists on social media and, since then, I have been steadily investing in the knowledge and equipment to produce high-quality images to present for informal consults on social media.

Fortunately, my trainers permit me to seek informal consults on cases that are difficult for us to unravel. These interactions have definitely boosted the quality of our practice.

HOW DID YOU ENCOUNTER X-WOW! AND YUCHUN DING?

I followed X-WOW! on Twitter (@X_WowCom) because the handle shares microscopic pictures. It was a stroke of luck that they came across my tweet on a thread where I was responding to the dictum, "The grass is always greener on the other side." I was defending my opinion that there is no grass on the side of the fence where I am. To explain why I felt this way, I offered a peek into all the struggles I put up with and the sacrifices I have made to get good pictures to share on Twitter. Over the years, I have taken out loans to purchase smartphones with high-quality cameras – not because I want a "fancy phone," but so that I can produce great quality pictures. I tried DIY mobile phone adapters for the microscope, but they didn't work out, so I eventually bought an adapter on AliExpress. Finally, I was able to get an Amscope microscope camera, which is what I use mostly for capturing my cases. I got a good computer and Adobe Photoshop software to edit my pictures – all in a bid to be excellent. I even



learned how to take and edit good pictures from social media, thanks to Phillip McKee (@phmckee1948) and Jerad Gardner (@JMGardnerMD), the first social media teachers I ever knew.

You might find it hard to believe that I never linked Yuchun Ding to X-WOW! – not until he contacted me about this article. X-WOW! asked me how they could be of help in my efforts, and I mentioned that I would appreciate a microscope, because that was the next thing on my lab "wish list." I am extremely grateful to him for shipping me a modern microscope. It's my first personal microscope and I am treating it with the greatest respect!

It arrived barely a week ago, but I can be sure of one thing: it will definitely increase my educational efforts. Now, I can work from home to take pictures and share them, rather than having to go to work just so that I can create and access images.

WHAT ELSE IS ON YOUR LABORATORY WISHLIST?

Like I said earlier, we operate at the most basic level you can imagine. My wishlist might seem simple to those with more sophisticated laboratories, but would contain key equipment:

- A grossing table
- An automatic tissue processor
- A modern embedding station
- A modern Hydra multi-head teaching microscope with a good camera
- More microscopes
- The basic equipment required to run an immunohistochemistry lab
- And, lastly, maybe someday a mobile slide scanner – but, right now, that seems like a luxury!

Much of our existing equipment is old, unserviceable, or nonfunctional, including our microscopes. As a result, the most valuable tool we have is human resources. My colleagues' – and my own – resilience, our desire to learn, and our need to make a difference in difficult situations is unrivaled.

WHAT DIFFERENCE CAN DIGITAL PATHOLOGY MAKE IN DEVELOPING COUNTRIES?

Based on my own time in the laboratory, I would say that digital pathology can bridge gaps in knowledge and experience between the underserved areas and the developed world in the form of specialist consults on difficult cases. In extreme cases where there are no pathologists at all in a given area, digital pathology can offer the "impossible" – bringing quality healthcare from thousands of miles away to meet those patients' needs.

Pathology in resource-poor settings can be repositioned through foreign aid, collaborations, training via telepathology, and technical support. If pathologists and laboratories in resource-limited settings had more access to good equipment, good training, and good collaborations, I believe that we would be able to deliver stellar services. Thanks to organizations like X-WOW! and Associazione Patologi Oltre Frontiera (a "pathologists without borders"-style non-governmental organization), some African countries are already receiving the assistance they need.

I would like to send my gratitude to those who devote their time, money, and resources to teaching colleagues in resource-poor areas. My passion for pathology was rekindled by my daily interactions on social media – so thank you to everyone who contributes!

Olaleke Folaranmi is Senior Registrar at the University of Ilorin Teaching Hospital, Ilorin, Nigeria.

PATHOLOGISTS WITHOUT BORDERS

Digital pathology can facilitate long-distance diagnosis and ease resource pressures

Michael Schubert interviews Peter Carey

HOW DID YOU AND YOUR COLLEAGUES GET INVOLVED WITH PATHOLOGY IN MALAWI?

Liz Molyneux, a distinguished pediatrician, and her husband, a malariologist, lived in Malawi for many years. She set up and ran the pediatric malignancy unit in Blantyre until they retired. One of my pediatric oncology colleagues here in Newcastle, Simon Bailey, is originally from South Africa; as a trainee, he visited the unit and went on to collaborate with Liz for many years devising protocols for childhood cancers, in particular acute lymphoblastic leukemia (ALL) and Burkitt lymphoma. Together, they adapted existing protocols to make them realistically deliverable in a resource-challenged setting. Their approaches might be slightly less intensive than conventional western medicine, but they've made it possible to treat these diseases in settings that have no other options. Simon and Liz have also diligently collected data, reported their experiences academically, and demonstrated that these treatment regimens are safe and effective, given the challenges of the settings in which they are administered.

"We've taught them to take photomicrographs with a CCD still camera on top of a microscope, so they can send us representative slides."

Simon would visit Blantyre once a year and return with boxes of slides. He would ask a friendly pathologist – usually me – to verify their diagnoses because they were writing up case series. We also performed immunocytochemistry and molecular tests on some of the material. Unfortunately, it was all retrospective. We only received slides once or twice a year, so we couldn't offer clinically useful information in a timely manner.

There is a pathology laboratory in Blantyre, but the turnaround times can be variable, so the pediatric team has learned to spread blood films, make smears of fine needle aspirates (FNAs), and spread slides from bone marrow aspirates. They can even do Romanowsky stains on the ward by dipping slides into the staining solution. We've also taught several of them to take photomicrographs with a CCD still camera on top of a microscope, so they can send us representative slides of peripheral blood, bone marrow aspirate, and FNA films.

HOW DOES REMOTE REPORTING WORK?

Initially, the team sent us emails with a few clinical details and a link to the slide images in Dropbox; I reviewed everything and gave them a report, including whatever helpful comments I had to offer. Because we could do it fairly quickly, it took off – and soon, we were receiving so many emails that they crashed into each other in our inboxes. That's when we realized we needed a more intelligent system to cope with the workload and the generation of reports. My colleague Stephen O'Brien, a professor of hematology here in Newcastle, is internationally known as an expert in chronic myeloid leukemia, but locally also renowned as a bit of a computer geek. We got him to build us an interactive website – so now, the Malawi clinicians can enter demographic and clinical details into an electronic "request form" on the site. The form also attaches a Dropbox link to the images, creates a reporting worklist, and sends an automated email alert to indicate that cases have been entered for reporting. I can go in to add comments on the morphology, add diagnostic coding, and Simon can add a clinical comment with any management suggestions. The result is an integrated report populated with everybody's contributions that gives the clinicians the health information they need and allows us to collect academic data as well.

The limitation, from a pathological point of view, is that I'm guessing based on half a dozen images of fields selected by a clinician with no formal pathology training. The advantage is that I can form an opinion quickly – but the downside is that I might not see something I would have found if I'd searched the whole slide myself. Now, though, we're approaching the era of affordable whole-slide scanning. We're currently limited by file sizes and creaky Internet connections, but I think sharing whole-

slide images will be feasible in the near future.

But with more material comes more work – and that's where X-WOW! is helping. Yuchun Ding has two key innovations. First, an inexpensive "scanning" method that involves driving the microscope around the stage with the still camera on to form a composite image using clever software. And second, still in progress, AI software to look at and categorize individual cells. The latter has been done commercially for peripheral blood, but with an expensive standalone system that resource-limited laboratories can't afford. Ding is working on affordable software to automate preliminary scan interpretation.

WHAT IS THE PATHOLOGY INFRASTRUCTURE LIKE IN MALAWI?

There is a laboratory service in Malawi, but it lacks the resources on which western labs often rely. As a result, machines may break down and not be repaired, sample storage and preparation can be a challenge, and turnaround times are often slow. These challenges particularly impact tissue biopsies, so the pathologists and laboratory medicine professionals have come to rely largely on liquid material.

Although they do have a local laboratory, the staff at Blantyre appreciate our complementary service because we're able to respond quickly when they don't have time to wait. Previously, they had to make a lot of decisions purely on clinical data, but now, we can confirm when they're doing the right thing, make recommendations when they need to change their approach, and flag specimens with too little material to make a definitive diagnosis.

Now that Liz has retired, the clinic at Blantyre is led by pediatric oncologist George Chagaluka. Staff are trained to acquire FNA specimens, bone marrow aspirates, and peripheral blood specimens, and to prepare material for pathological assessment. Simon and his team go out each year to refresh that training, and we've also provided them with a blood count machine that allows them to operate as independently as possible. It's true that they have limited resources, but they're overcoming that obstacle and maximizing their ability to use what they have.

HOW DID YOU ENCOUNTER X-WOW! AND YUCHUN DING?

I met Ding when he was working with Chris Carey (no relation!), a hematologist with an academic interest in lymphoma. The two of them began to collaborate on software to look at images of lymphoma tissue, and that has blossomed into something larger. Ding came across the Microvisioneer software, which enables still camera "scanning" for far less than the price of a slide scanner. It was immediately clear that it would help resource-limited laboratories; although it's more time-consuming for the operator, it captures a more comprehensive area of the slide. That way, pathologists doing remote reporting don't have to worry about missing anything of diagnostic significance because it wasn't represented in a few still photos of a slide.

I think full implementation will take some time. The staff at Blantyre already have the software, but they're accustomed to taking still photographs, so they may need in-person training before they're equally comfortable using the camera as a "scanner." Hopefully, if a case arises in which we need to see more, they'll try the new technique. In the meantime, we're giving Ding lots of scanned images to build up his AI software, so that when we start receiving whole-slide scans regularly, they don't consume all of our time. The goal is for the information increase to be offset by the new software.

WHAT IS THE FUTURE OF PATHOLOGY IN RESOURCE-POOR AREAS?

Let's say a new child comes to a western hospital with ALL. We might be able to look at a blood sample and say, "Here are cells compatible with a population of lymphoblasts" – but we would never make a diagnosis or start treatment without an immunophenotype and additional genetic data. In Malawi, they don't have access to that information, so they treat based on what they can find out.

But on occasion, for particularly interesting patients, the staff at Blantyre have put a drop of blood onto blotting paper and sent it to us to extract DNA for molecular analysis – for instance, to find a Philadelphia translocation or a *BCR-ABL* or *PML-*

RARA fusion. We've been able to bypass immunophenotyping entirely and go straight to molecular analysis, because the necessary material is potentially transportable and the technology works quickly. Immunophenotyping equipment is expensive and presents a training challenge, whereas material for molecular analysis can be transported far more easily and we can do the analysis from a distance. I think the biggest challenge in that arena will be transporting, extracting, and analyzing DNA in a timely fashion.

In the meantime, I think digital pathology is making a huge difference – particularly with the newfound ability to do whole-slide scans in resource-limited settings. An example that struck me recently came from pathologists doing remote reporting for China, where it's not culturally appropriate to export human tissue beyond the border. If a Chinese pathologist wanted to consult someone in America, they couldn't send a block and ask for an opinion. What they do have, though, is fantastic immunohistochemistry and slide preparation techniques – so they were able to do that locally, scan it, and send the scans to pathologists in other countries. In the end, reporting those scans was no different to reporting material obtained locally.

"Digital pathology means that it doesn't matter where you are geographically; you can still provide a top-quality service."

The problem is that many places have a shortage of trained expertise. If experts don't have to move geographically to be useful, jobs become more attractive and they can even take several part-time positions in different locations to make up one full-time job. Digital pathology means that it doesn't matter where you are geographically; you can still provide a top-quality service from a long way away. As long as you have people to acquire and stain the material, you can export everything else.

WHAT ELSE IS ON THE "WISH LIST" FOR A RESOURCE-LIMITED LABORATORY?

In terms of hematology, the first thing you need is decent, reliable blood count information. Next, you need people skilled enough to prepare the material. They need to make good blood films, acquire and spread FNAs and bone marrow aspirates, make Cytospins of liquids, and stain reliably. Even in the UK, staining techniques vary considerably. I'm pleased with the staining machines our lab currently uses, but I remember tearing my hair out for several years, shouting up and down that I was getting better quality from Malawi via a few photographs than I was getting out of my own laboratory!

The next big thing on the wish list is a better method of acquiring images. We've moved on from still photographs and are now encouraging the software-based "scanning" approach – but it's still a bit clunky. One day, I hope every lab will be able to pop slides into a box that does the job automatically in minutes – first one slide at a time, and then with racks that accommodate multiple slides. Scanners are growing increasingly affordable, so it's not out of the realm of future possibility.

WHAT ADVICE DO YOU HAVE FOR LABORATORIANS IN RESOURCE-LIMITED SETTINGS?

It's good to have trained people on the ground who can gradually improve the service. We can help with that by offering training positions. It's increasingly difficult for people to obtain international travel funds, visas, and so on, so it's vital to have enthusiastic local staff. They can pass on their knowledge to newcomers and ensure that the cycle of well-trained physicians and laboratory staff continues. That also ensures that they maintain the skill of preparing decent material; if you have to not only teach others how to do it, but also report it yourself, I find that it makes you care more about the quality of the material.

We're running a service for a relatively small children's facility, so we've been able to stay on top of the workload. However, when the same services are offered on a broader scale, or when we handle more data (for instance, by receiving whole-slide scans instead of single photographs), we will need much more manpower. That's when we'll need either the assistance of AI or more people reporting. Luckily, digital pathology means that we can give more people access to the diagnostic information – and it doesn't matter where they are in the world. Anyone can chip in and help – and that's the real power of digital pathology.

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On *NTRK* and Other Fusion Biomarkers

How next-generation sequencing can change cancer's future

An interview with Fernando Lopez-Rios

NTRK fusions are rapidly gaining attention in precision oncology as therapies that target these rearrangements are becoming available. Not only are these treatments evincing marked clinical responses – described as "amazing" – but they are doing so in tumor types and clinical situations that constitute a significant unmet patient need. But it also brings new challenge for pathology laboratories. Dr. Lopez-Rios tells us more…

Is NTRK fusion detection part of the routine testing algorithm today?

Yes and no… Nowadays, *NTRK* is included in NGS panels used routinely in some laboratories, but it's rarely tested as an individual biomarker. This needs to change in the near future, and many more patients should have access to *NTRK* testing. One possibility proposed by the recently released ESMO guidelines (1) is to use immunohistochemistry to screen for *NTRK* rearrangements and then confirm all positive results with NGS. This is a sensible approach to take until NGS technology reaches the point where we can use it for every patient.

How will NGS testing fit into existing workflows?

You start with a question – is the histological tumor type known to harbor a highly recurrent *NTRK* arrangement? If the answer is yes, then there are several things that you can use: fluorescence *in situ* hybridization (FISH), real-time PCR (RT-PCR), or NGS to confirm it. But if the answer is no – and you have a sequencing platform available – you should consider using NGS up-front. If you don't, then you start with IHC and confirming positive cases with NGS.

Laboratories that still perform individual biomarker tests will likely continue to do so with the addition of *NTRK* IHC. Those already performing NGS won't need to change anything; they'll just need to ensure that they are targeting all three genes.

What about fusion biomarkers in general?

Overall, the role of gene fusions in precision oncology is increasing. There are either clinical trials or established treatment options available for patients with *ALK, ROS1, NTRK, or RET* translocations, so having sequencing information is clearly invaluable.

Is there enough evidence to argue for the use of NGS in all non-small cell lung cancer patients?

I think there's no question that NGS makes a lot of sense for NSCLC because there are multiple clinically relevant biomarkers and several drugs per biomarker. In other tumors, NGS is still sometimes seen as a "last resort" because it's used to identify patients for clinical trials, so we may have a harder time convincing our clinical colleagues to use first-line NGS in those instances.

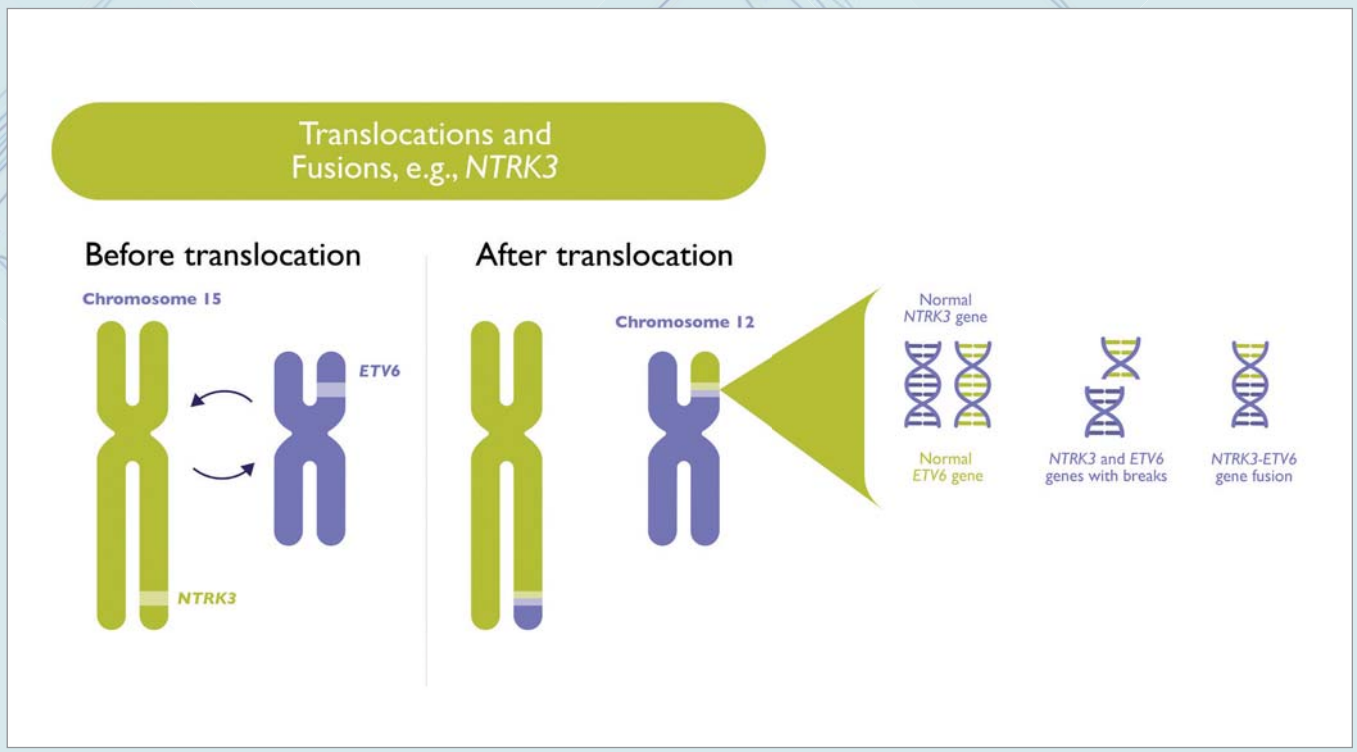
With the arrival of *RET, NTRK,* and other druggable gene rearrangements in lung cancers, I think the balance will shift toward up-front NGS in increasing numbers of patients. At the moment in our laboratory, the split is about 50/50 – but, every year, I estimate that NGS increases by 10 percent. So I think the question is not, "How will this fit into the current lung cancer workflow?" It's, "How will this change the current lung cancer workflow?"

"With the arrival of RET, NTRK, and other druggable gene rearrangements in lung cancers, I think the balance will shift toward up-front NGS in increasing numbers of patients."

What challenges does NGS fusion testing still face?

The biggest challenge we have at the moment is obtaining high-quality RNA. I'm not worried about the quantity, because everyone in the cancer care pipeline – from surgeon to oncologist – is now aware of the need for larger sample sizes, but the quality of the RNA is still a problem. Our current failure rate is in the 3–5 percent range; it's not huge, and I'm optimistic that we can improve on it.

We cannot report an advanced lung cancer without fusion testing results, so in cases where NGS testing fails due to sample quality, we rely on FISH or IHC to give us the answers we need. I think we also need to make changes to the workflow to reduce turnaround times



and eliminate the need to batch patients. This last remains a challenge because, with the way existing products are presented and the way chips are designed, it's difficult to overcome this barrier.

Much has been written about what NGS technology is best for fusion detection. What are your thoughts?

There are several lines of evidence demonstrating that RNA-based NGS is preferable. DNA-based NGS is associated with a significant risk of false negatives (2).

"Overall, the role of gene fusions in precision oncology is increasing."

What does the future of NGS look like?

I am convinced that, in the future, we will have "real-time NGS." By that I mean two things: one, that we'll have the flexibility to start running a patient sample at any point. Currently, with IHC, we have machines with as many as 30 different chambers, each one of which can run separately so that each sample doesn't have to wait for the previous one to finish – and I think we'll have something similar in the future for NGS (i.e., a continuous workflow). And two, that we'll have a short turnaround time. For me, the dream turnaround time would be 72 hours, which is doable, but at a significant cost. In the future, I think we'll be able to bring the cost of rapid sequencing down. Given the number of patients who can benefit from comprehensive profiling, NGS becomes an economy of scale.

Right now, we can take a blood draw or a biopsy and return an RT-PCR result in a few hours. Some predictive IHC assays take very little time. Who knows? Perhaps one day, NGS will provide results within a single working day as well.

Fernando Lopez-Rios is Head of Pathology and Targeted Therapies Laboratory, Hospital Universitario HM Sanchinarro, Madrid, Spain.

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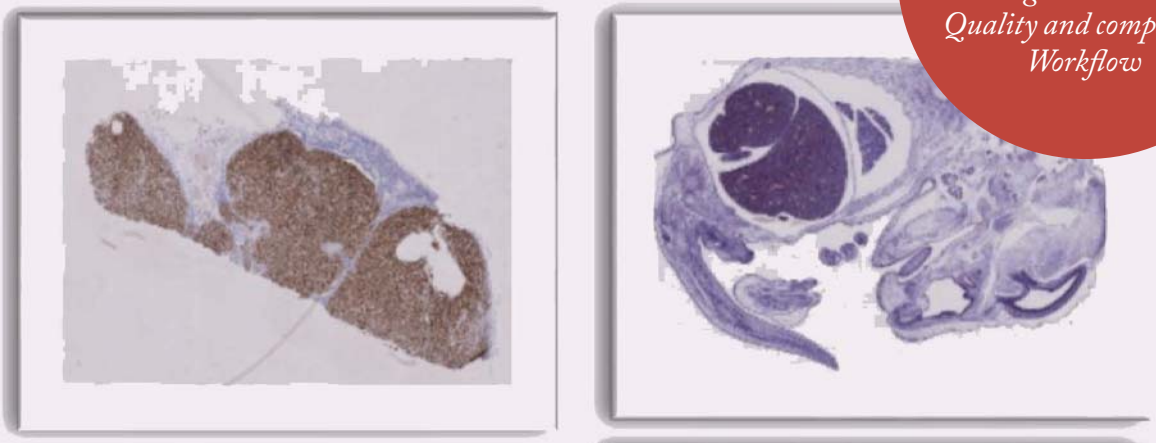
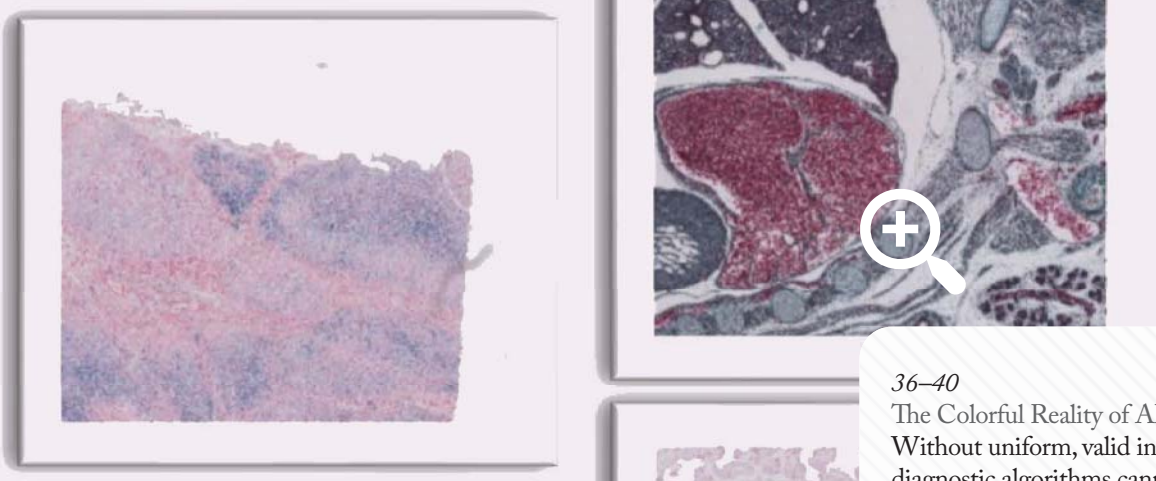




In Practice

Technologies and techniques
Quality and compliance
Workflow

The Colorful Reality of AI

Why color standardization of whole-slide digital imaging is essential to reliable computer-aided diagnosis

By Richard Salmon

Look around you and you'll appreciate that "color management" is applied to a broad mix of everyday technology – from televisions to cameras; industrial label presses to cinema screens. Accurate, reliable color is deemed so important that these industries take extensive steps to mitigate any reduction in its performance or appearance. The integrity of color in medical images should be no different – in fact, given the implications of the technology, it's where standards should be the most stringent of all!

Color critical

Different stains are applied to histology samples so that we can visualize important detail and specific tissue features using bright-field microscopy. Consequently, histopathologists use a wide range of colors to identify the presence of biomolecules, cells, and structures (see Figure 1). Tissue is precisely and selectively stained; the different colors are not deployed at random, but are selected to ensure effective diagnosis.

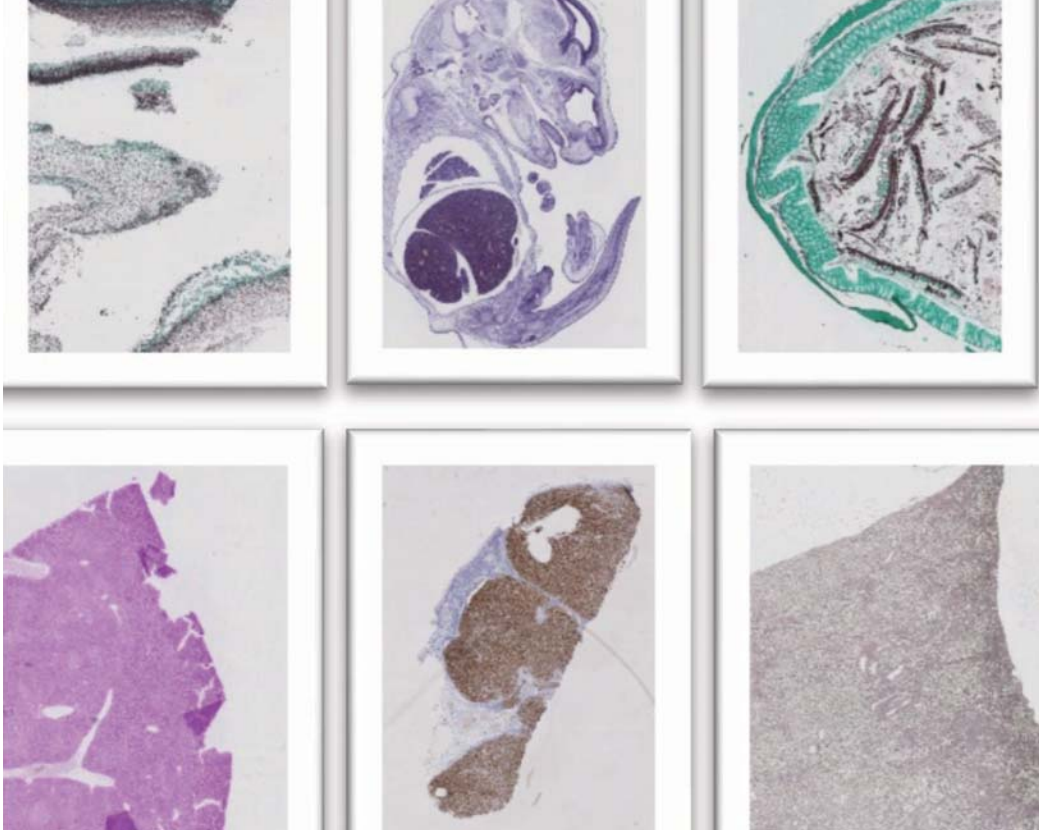


Figure 1: Histopathology has a wide range of colors that must be accurately digitized by WSI scanners.

The introduction of whole slide digital imaging (WSI) devices has great potential to improve medical diagnosis. However, each WSI scanner can be thought of as a unique arrangement of optical and digital components, which means that the digital image created varies from one device to the next. These differences are evident not just between manufacturers, or even across product portfolios, but even between individual scanners of the same model – a challenge that carries significant implications, including a lack of accurate, uniform color.

That's why pathologists are calling for WSI scanner color to be measured and calibrated. As well as boosting users' confidence, this will have positive implications for the development of high-accuracy digital pathology artificial intelligence (AI), with the ultimate goal of ensuring that data processed by computer-aided diagnosis and AI is standardized.

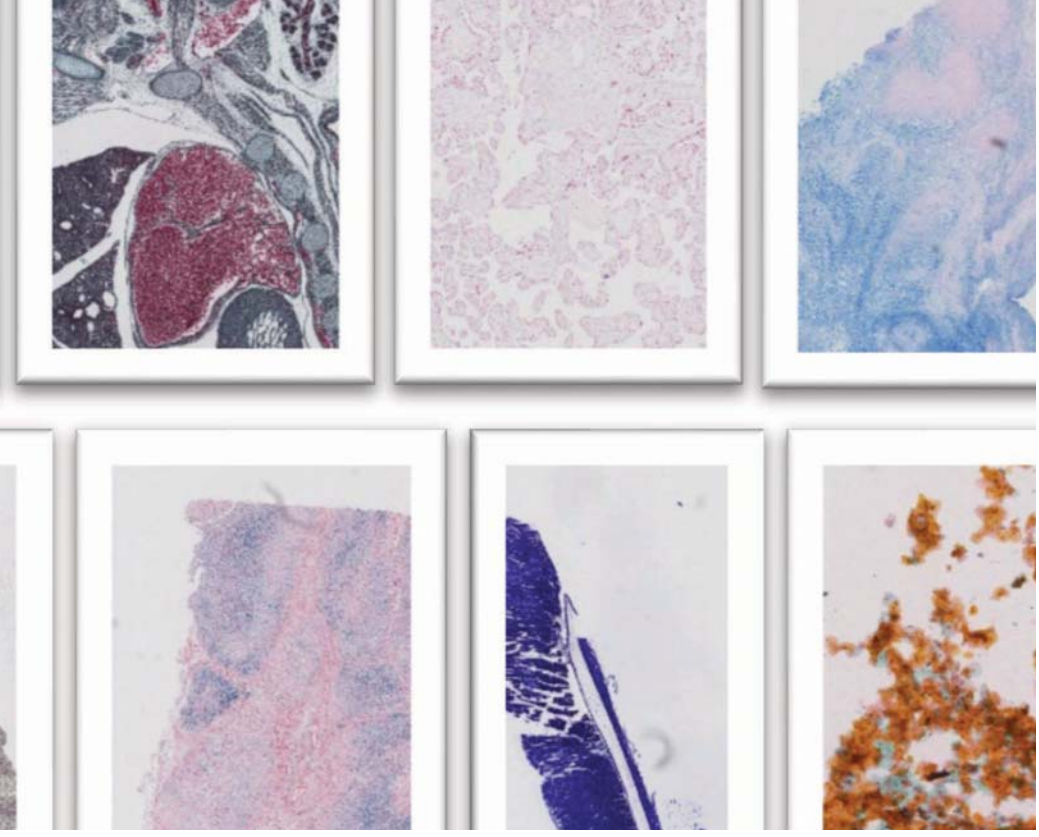
In fact, this issue is deemed important enough for both the UK's Royal College of Pathologists and the US Food and Drug Administration (FDA) to include in their best practice recommendations for implementing digital pathology. In procuring WSI devices, the College states, "Pathologists may wish to include assessment of color accuracy in their testing" (1). The FDA goes one step further to detail how color differences between WSI devices should be addressed. Their recommendation reads, "The WSI system should be tested with a target slide. The target slide should contain a set of measurable and representative color patches, which should have similar spectral characteristics to stained tissue" (2).

The AI effect

Many factors have an impact on the accuracy of AI. Inconsistencies in data format and content reduce its ability to accurately categorize and quantify information, compromising decisions that must be accurate and appropriate. In the case of digital pathology AI, the potential impact of such inconsistencies could be, at best, delayed diagnosis and potential disease progression. At worst, it could result in misdiagnosis,

At a Glance

- *Color management is vital for many technologies – but none so much as histopathology*
- *Features of digital images, such as color, vary between scanners*
- *Because color is not standardized between devices and images, AI algorithms may not perform as accurately and reliably as they could with uniform input*
- *One approach to achieving uniformity involves the use of a special slide to standardize devices to real-world histopathology colors*



ineffective treatment selection, and, ultimately, life-changing or even life-limiting consequences.

The different colors present in precisely and selectively stained human tissue are essential to accurate diagnosis. And that's why it's vital to not only train AI software to recognize spatial data, but also ensure the ongoing accuracy of input data and therefore decision-making reliability. This can be accomplished at least in part by working toward consistent, standardized color for digital images across WSI device types. It's no easy task, especially when you consider that – despite knowing that color differs between WSI devices – data from multiple devices is used for the same AI/diagnosis. Until this issue is addressed, any analysis undertaken uses potentially compromised data. After all, we're all aware of "garbage in, garbage out" – the idea that if bad data is put into AI systems, they will return equally bad results.

Some AI developers have adopted (or developed their own) workarounds to the computational handling of color inconsistencies. Those may work as stopgap measures – but why should laboratories divert brainpower, time, and resources to solving a fundamental issue that scanner vendors should address? Their time would be better spent focusing on the critical task of enhancing computer-assisted diagnosis.

Current approaches to color management

Interrogation of data at the machine-learning or deep-learning level requires a different approach to color interpretation. For instance, color segmentation can assess the approximate spread of color data in machine-learning applications, which allows users to address batch variation by normalizing individual stains to a custom color space. Within deep-learning AI approaches, histograms of individual color distributions are assessed at the pixel level for high-precision intra-image correlation. Such approaches can flatten and smooth color variation at the subcellular (non-spatial) level.

Although these methods offer fine control and measurement of color spread, they are limited by the extremes of data provided. Not only are the image input and the altered output likely to differ significantly, but neither is representative of the real, ground-truth tissue sample. Data is presented from intentionally and specifically stained samples to the AI to assist with diagnoses; bypassing or manipulating the color aspect could alter or entirely miss a piece of biological truth.

False coloring is most commonly used in image analysis to flatten variations between samples by artificially applying non-reality-standardized characteristics to cellular structures, which allows us to feed the AI uniform data. However, it is the most basic way of dealing with color and, in effect, ignores the existing color altogether. And so, all color-specific data (spectral truth, intensity, and density) and the biology it represents is compromised. Instead, the focus is exclusively on the spatial data of tissue structures – meaning that we have less than 100 percent of the available data and, worse yet, less than 100 percent of the data we need for a complete diagnosis.

Emerging techniques

Newer and more specific techniques have emerged, aimed at increasing the accuracy of computer-assisted diagnosis. The goal is to allow universal AI on images from differing clinical and scanner sources. Of particular note is the translation of color from pre-existing applications by Cycle Generative Adversarial Networks (CycleGANs).

In Figure 2a, a CycleGANs image algorithm has been used to maintain the spatial information of a zebra and orange (representing cells and tissue, respectively) while converting color to simulate an image of a horse and apple (synonymous to digitally converting specific stain color) (3). In Figure 2b, the same technique has been applied to a mountain landscape, changing it from a summer to winter scene. In this context, the algorithm could be used for marketing purposes such as tourism to make the same location influence different traveler personalities. "Counterfeiting" images in such a way could be considered misleading – but, in advertising, communication, or media arenas, that carries only minor

Figure 2. a) Zebras and oranges ("tissue") converted to horses and apples ("staining") by CycleGANS.

Figure 2. b) CycleGANS can influence perception of an image, transforming a serene lakeside retreat into a challenging mountain to climb.

implications. In medical diagnostics, on the other hand, actively manipulating an image containing medical data prior to diagnosis has significant implications because you're altering life-critical data.

From a practical point of view, emerging evidence indicates that applying CycleGANS to tissue images from multiple scanner types improves the accuracy of pre-existing AI tools. This technique could normalize colors received from different scanners to a standard color space, rather than making them appear as something different entirely. However, different algorithms work to different accuracies (4), meaning that this methodology is still susceptible to high degrees of variation and that its output is still artificially constructed. Ethical issues aside, the fact that simply changing the color of scanner X images to match those of scanner Y results in increased AI accuracy indicates that color is a significant influencer on digital diagnosis.

This recognition of color's importance for refining AI accuracy is met by the recent development of color-standardizing algorithms that can be used as a pre-diagnostic method (5). These create a deep-learning color-handling tool for analysis, using extensive, pixel-level color and spatial analysis to separate the specific stains co-located in a single pixel. They are then combined with established chromatic data for each stain component, allowing the application of hue/saturation/density relative to the entire WSI from the pixel level. The result? A universal standardization algorithm that has the potential to be applied in combination with developed (or developing) AI tools to generically increase computer-assisted diagnosis accuracy through digital color management.

This major step forward recognizes and mitigates the effect of color on the pixel, spatial, and cross-sample level of big data analysis – but it's not the end of the road. The core definition of color is still from inferred data only, and doesn't encapsulate the absolute truth held within each tissue sample. Absolute color truth in WSI images can only ever be addressed by a direct, real-world, scanner-specific measurement.

A firm grounding in reality

A key message emerges from these different AI approaches: color uniformity and reliability are important for maximizing AI accuracy. Although there is no denying that spatial data on cellular distributions in tissue is the main driver for all diagnosis, it may not completely dominate the computer-assisted diagnosis landscape – as evidenced by CycleGANs, where transformation to a standard color by scanner-to-scanner mimicry "flattens" color variation.

Such a realization may not seem significant at first; after all, if color is the only thing that changes, we maintain the inevitable image quality variation – focus, stitching, and resolution – that arises from using two different imaging systems. But, even though the differences in non-color data quality should negatively affect analysis if spatial data were the only driver, it appears that CycleGANS enhance, rather than diminish, AI accuracy.

As effective as post-imaging data-handling techniques may be, none fully embrace the FDA's recommendations, nor do they enable AI solutions to use "ground-truth data" that captures all scanner-to-scanner, image-to-image reality. When the original color is consistent between scanners, we're likely to see even further improvement.

An alternative approach is to use International Color Consortium (ICC)-standardized color profiles to calibrate WSI devices. This method involves using a slide with a number of histologically stained patches that precisely mimic stained tissue to measure the spectral absorption of commonly used pathology stains. Measurements are then combined with each scanner's color interpretation of the same slide and the interpreted error (the scanner's individual deviation from a standard truth) calculated. ICC profile metadata is then generated and used to correct the pre- or post-imaging output so that the digital image contains ground-truth color.

The color is not only closer to truth, but also unified across all scanners. For AI software, the key advantage is the application of such calibration technology on a regular basis to ensure that decisions are made based on uniform input, and that all images, irrelevant of source, remain digitally unaltered and are quality-controlled to be ground truth color as standard.

To demonstrate the impact of color management using this ground-truth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calibration slide method (6), color error can be reduced by a factor of more than 700 (see Figure 3), which raises two big questions. First, this is medical technology – is it acceptable for a medical device to have more than 700-fold error in any aspect of its function? And second, the downstream use of AI is human-free – do we trust decisions made on data that either has 700-fold error in a major component or is artificially manipulated by algorithms to satisfy a successful outcome?

Within the lifetime of anyone reading this article, medical imaging and AI have made huge advancements toward automation. To achieve this degree of computer-assisted diagnosis accuracy and reliability, we have liberated more layers of data buried within each WSI. However, AI consequently requires increased data quality and validation stringency. The discrete color of a tissue sample represents the molecular-level interactions at which refined pathology with cutting-edge precision can be performed. AI's ability to cope reliably with color variation between WSIs and to create a uniform interpretation of these differences has shown clear improvements in preclinical AI, increasing its application to large and varied datasets.

Color management is a fine-edged tool that makes AI commercially competitive and reliable. But AI still has its limitations; any computational color-handling is no more than data manipulation with varied degrees of success. The ground-truth colors in pathology are real data from real patients who require diagnostics based on reality. Only by using color management techniques with the ability to create standardized, ground-truth colored images irrespective of WSI scanner source will AI truly be able to offer complete color certainty to assist with life-changing medical decisions.

There's no denying that the AI future is coming… but when it comes to the ultra-precision offered by color management, AI must be firmly grounded in reality.

Figure 3. Errors in color before and after slide-based color management of three different WSI scanners from different vendors. In some regions of the gamut, color error was reduced by 700-fold or more.

Richard Salmon is Product Manager for Life Sciences at FFEI, Hemel Hempstead, UK.

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A Better Future for Bladder Cancer

A new biomarker allows effective, noninvasive screening of patients at risk of the disease

By John Cucci

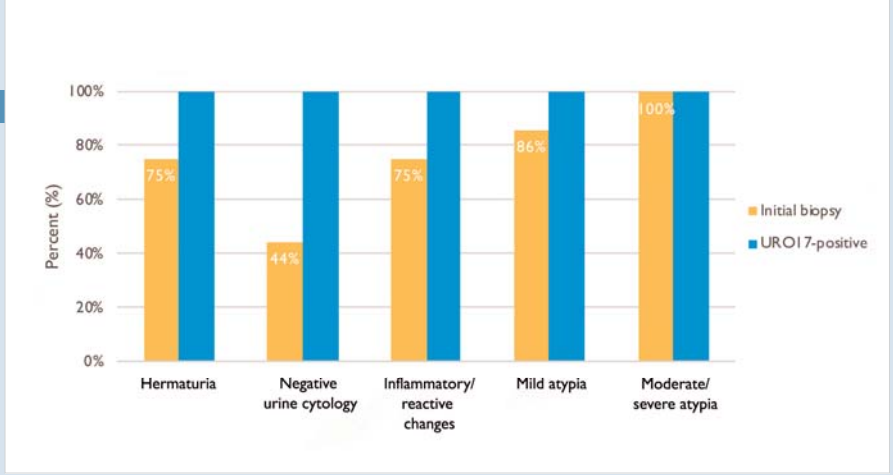

Figure 1. Accuracy of UROI7™ in diagnosing urothelial carcinoma (UC) in patients at risk of the disease. Among 39 cases with final clinicopathologic diagnosis, UROI7™ ICC was positive in all 39 cases. At least 10 immunoreactive urothelial cells were detected in each cytologically malignant urine specimen with biopsy-confirmed UC.

Bladder cancer presents a diagnostic challenge for even the best pathologists and laboratory medicine professionals. With symptoms similar to those of other urinary tract conditions and no reliable screening tests to spot malignancy, patients may experience delays in diagnosis. And these delays can affect survival – almost 90 percent of those diagnosed at stage I survive five years or more, whereas only about 10 percent of those diagnosed at stage IV achieve the same survival. To provide patients with the best possible chances, diagnostic professionals need sensitive, specific tests for bladder cancer – a problem to which UROI7™ offers an effective and noninvasive solution.

The promise of UROI7

A sensitive and specific biomarker for bladder cancer, UROI7™ is a noninvasive, cost-effective diagnostic tool (1) that I believe can revolutionize how the disease is detected and treated (see Figure 1). It is currently being used in conjunction with traditional urine cytology, which requires a simple voided urine collection and is indicated for patients at high risk for bladder cancer.

Urine cytology, traditionally the most commonly used test for bladder cancer, is largely ineffective; its sensitivity for the disease is below 40 percent and the American Urological Association (AUA) has even advised against its use as part of the routine evaluation of microhematuria. Another commonly used diagnostic testing methodology, fluorescence in situ hybridization (FISH), can detect chromosomal abnormalities linked to bladder cancer – but although it offers more reliable results than cytology, FISH is significantly more expensive and remains ineffective at detecting low-grade tumors.

In published studies, UROI7™ has proven to be highly sensitive and specific, achieving a sensitivity of 100 percent and specificity of 96 percent in urine specimens and a sensitivity of 89 percent and specificity of 88 percent in tissue specimens (2). In addition, the marker identifies both low- and high-grade tumors at a significantly lower cost than FISH.

Real world use

Who might be suitable for UROI7™ testing? Anyone suspected of being at risk for bladder cancer. If a patient experiences gross or microscopic hematuria, frequent or painful urination, exhibits any familial or historical risk, is a smoker, or is over 50, then it is worth testing for the disease. Prevention is better than a cure.

As an immunocytochemistry (ICC) stain, UROI7™ can easily be incorporated into any lab's bladder cancer detection program. Most labs already have the instrumentation required to run the marker in-house, so adding UROI7™ testing should not cause any workflow issues. However, for those not yet prepared to bring the test fully in-house, UROI7™ is also available on both a technical component (slide preparation only) and global (final report issued) basis – and when laboratories are ready to take the next step, Acupath is happy to assist with every step of that process.

Next steps

Since its debut, the UROI7™ test has taken off and the feedback has been overwhelmingly positive. Why? Because urologists, pathologists, and laboratory professionals all recognize the significant shortfalls of traditional urine cytology testing. Providers are eager to leverage this new tool, especially considering its noninvasive collection, cost-effectiveness, and minimal (if any) disruption to workflow.

Because the AUA has discouraged the use of urine cytology in recent years, many urologists have significantly decreased their reliance on it or stopped ordering it entirely. UROI7™ offers the opportunity to significantly improve on traditional urine cytology without the need to subject patients to a painful and invasive cystoscopy. I believe that UROI7™ will give us back the ability to noninvasively screen for bladder cancer – with the assurance that we can trust the results we receive.

John Cucci is Chief Sales Officer at Acupath Laboratories Inc., Plainview, USA. Acupath offers UROI7™ through a semi-exclusive licensing agreement with KDx Diagnostics Inc., Campbell, USA.

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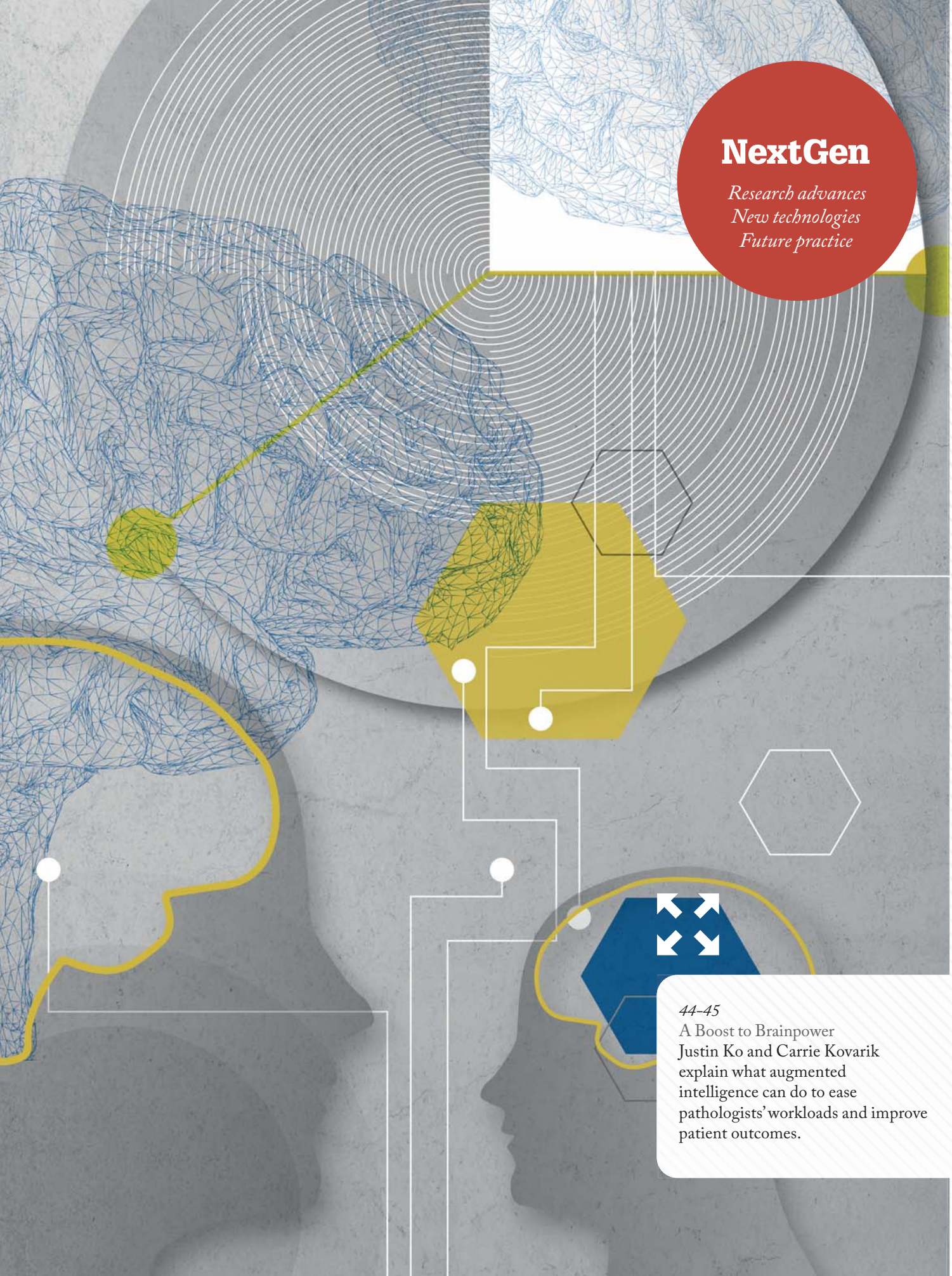

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A Boost to Brainpower

Enhancing the pathologist through augmented intelligence

By Justin Ko and Carrie Kovarik

Augmented Intelligence (AuI) has the potential to transform the clinical practice of physicians – and specialties with significant image-based components, such as radiology, dermatology, ophthalmology, and pathology, are uniquely poised to benefit from advances in deep learning applications. The concept of AuI focuses on the role of artificial intelligence (AI) in assisting clinicians. The goal? Not to replace human intelligence, but to enhance it.

Recognizing this potential, the American Medical Association (AMA) published its first policy to guide engagement and growth in this field in June 2018 (1). To ensure safe, effective, and equitable use of (and access to) AuI, the AMA seeks to:

- ensure that improved patient outcomes and provider satisfaction are priorities,
- integrate practicing physicians into the development of AuI,
- promote development of thoughtfully designed, high-quality, clinically validated AuI,
- encourage education for all stakeholders to promote greater understanding of the promise and limitations of AuI, and
- explore the legal implications of AuI.

Recently, the American Academy of Dermatology approved a position statement affirming that the key to realizing AuI's promise is twofold: one, to ensure that the technology is collaboratively developed and designed for the benefit of our patients, physicians, and the healthcare system at large; and two, to minimize the risk of potentially disruptive effects and unintended consequences (2). In dermatopathology, AuI tools and systems have the potential to enhance workflows and efficiency, support the ability to spread expertise and collaboration to those with limited access, and improve the predictive and prognostic power of traditional pathology approaches – all essentially supporting the specialist's capabilities.

Enhancing efficiency, workflows, and access

The movement toward whole-slide imaging and slide digitization forms the foundation that empowers AuI-based solutions. It can foster collaboration, communication, and access through dissemination of expertise. Expanding our diagnostic capabilities to medically underserved or resource-constrained areas can reduce traditional barriers and facilitate consultations. Additionally, AuI tools can potentially help identify similar slides in an archive or repository of previously diagnosed cases as a means of extending expertise. Currently, telepathology overcomes some obstacles through store-and-forward imaging, robotic telepathology, or slide scanning; however, these methods are often limited by local bandwidth, tissue processing, manpower, local expertise, and cost (3).

In addition to improving access to pathology services, AuI has the potential to improve efficiency and reduce dermatopathologists' workloads. An AuI virtual assistant could sort work based on complexity, highlight and identify features of interest on a slide, and allow pathologists to spend more time on cases requiring increased attention while simultaneously expediting assessment of more routine cases (4). Through deep learning approaches, AuI can also evaluate tumors based on diversity of nuclear features to help risk-stratify patients (5). Emerging efforts have demonstrated potential in evaluating deep learning methodologies on whole-slide images to augment decision-making (6,7).

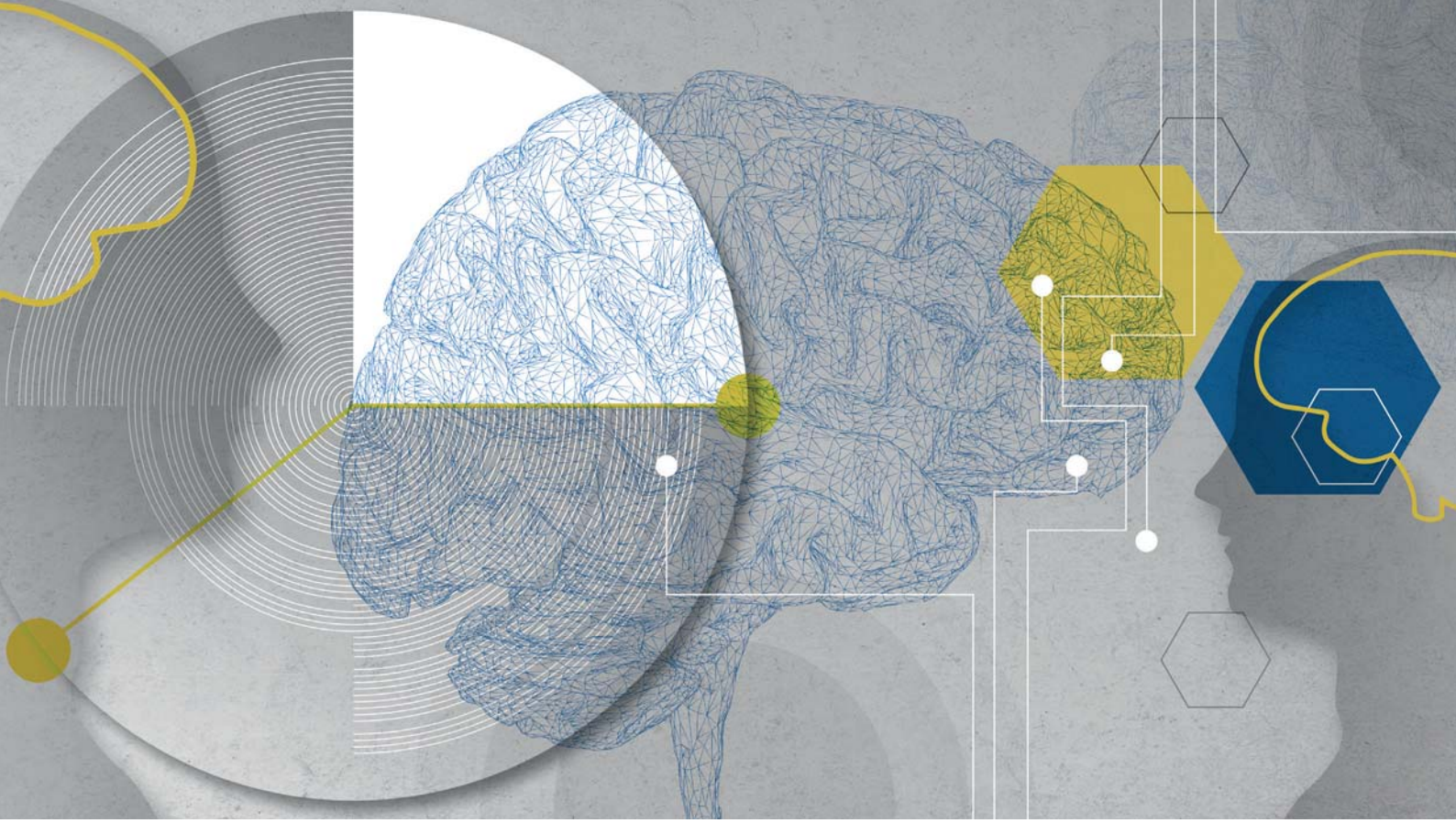
Future capabilities with more robust data and computational pathology approaches may enable AuI-based platforms to perform quantitative image analysis, identify features "hidden" to human perception, and make them available for consideration (8,9). One practical result of these capabilities may be the reduction of inter- and intra-pathologist variation.

Uncovering novel relationships

The foundation and gold standard for dermatopathology diagnosis has always been the pathologist's evaluation of tissue under the microscope. However, AuI's ability to integrate and analyze complex streams of multimodal data (combining tissue histology, molecular outputs from diagnostics and next-generation sequencing, clinical images, and electronic health record data) may uncover clinical relationships to enhance predictive and prognostic power (10). For instance, molecular profiling techniques have proliferated in melanoma, and the incorporation of validated and reliable tumor-level genomic information with clinical and outcomes data may hold

At a Glance

- *Image-based medical specialties – for example, dermatopathology – are uniquely poised to benefit from advances in augmented Intelligence (AuI)*
- *AuI tools must be carefully designed and validated to minimize disruption or unintended outcomes*
- *The tools must also be thoughtfully integrated into existing workflows to achieve increased efficiency and ease laboratory burden*
- *Only through human-centered design around the pathologist can AuI succeed*



the potential to predict future disease behavior and treatment response (11). Future approaches may even allow more fine-grained insight into protein–genomic associations and tumoral and stromal heterogeneity by tying molecular classification to immunohistochemical features (12). A dermatopathologist's augmented ability to analyze, synthesize, and interpret additional streams of information may support timely, actionable, and precise diagnoses for patients.

Although a future in which dermatopathology transforms from a tissue-centered clinical science into an informatics science incorporating non-tissue data streams may look different, the core of the discipline will not change. It will still be our charge to support clinicians' ability to make diagnoses and choose effective treatments for patients. However, AuI's ability to impact dermatopathology will depend as much on the thoughtful development and integration of such tools and systems as on the underlying technology itself. At the moment, dermatopathology AuI diagnostics have been subject to only the early stages of research, and they must be rigorously tested and validated in a wide variety of diseases before we can move forward. However, the promise they show is worth the effort.

Overall, pathologists have generally positive attitudes towards AuI, with nearly 75 percent of respondents in a recent large global study reporting interest or excitement in using it as a diagnostic tool (13). However, even within this optimistic cohort, there was concern for potential job displacement and replacement. Therefore, it is essential for human-centered design, with the pathologist at the core of AuI-assisted diagnostics, to lead the way to better care and outcomes and perhaps greater fulfillment and satisfaction with pathology practice.

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Carrie Kovarik is Associate Professor of Medicine and Associate Professor of Dermatology at the Hospital of the University of Pennsylvania, Philadelphia, USA.

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(AI) Trial and (Diagnostic) Error

How can new healthcare technology help address the number one patient safety issue?

By Thomas Westerling-Bui

The Emergency Care Research Institute (ECRI) recently published their 2019 patient safety report outlining the top 10 concerns affecting patients across the continuum of care. Using information from their patient safety organization database, root cause analyses, and votes from a panel of experts, the ECRI creates the list to help healthcare organizations identify and respond to new patient safety threats.

For the second year running, the 2019 report names diagnostic error as the number one patient safety issue, stating, "When diagnoses and test results are not properly communicated or followed up, the potential exists to cause serious patient harm or death." More specifically, the briefing scrutinizes the management of test results using electronic health records. "Providers have begun relying on the electronic health record (EHR) to help with clinical decision support, to track test results, and to flag issues. However, the EHR is only part of the solution," the report says.

At a Glance

- *Diagnostic errors were recently named the number one issue in the 2019 ECRI Patient Safety Concerns report*
- *Artificial intelligence (AI) can help to detect and mitigate these errors*
- *Using AI for image analysis frees up time for pathologists to carry out the tasks that require the most skill*
- *Broader adoption will help produce real-world evidence supporting the role of AI in improving patient safety*

Diagnosing diagnostic errors

To understand how we can combat and prevent diagnostic error, it's important to appreciate how and why they occur in the first place. We don't understand everything about every disease process – and what we do understand is based on our knowledge of the average person. But, as diagnosticians are all too aware, disease is highly personalized and influenced by a plethora of factors – so what holds true for one patient may be inaccurate for another.

The term "diagnostic error" can describe a range of mistakes, from a wrong assumption due to incorrect self-reporting from a patient to the use of an unsuitable diagnostic test. The multidisciplinary aspect of modern medicine – although beneficial in many ways – can sometimes cause complications because of the huge team of doctors who need to work together to make a diagnosis. Overdiagnosis is also a major issue and often results from the unnecessary use of diagnostic tests, which increases the number of patients who receive a false-positive result.

As a result, achieving the correct diagnosis 100 percent of the time is almost impossible. Diagnostic errors are an inevitable consequence of the heterogeneity of human disease and, rather than attempting to prevent them altogether, the most effective strategy is to detect, monitor, and mitigate these types of errors to minimize their impact on patients. And that's where a range of emerging healthcare technologies can play a crucial role.

The AI solution

One of the ways that technology can alleviate diagnostic error is with image analysis, in particular with the application of artificial intelligence (AI) to the analysis of certain assays. Cases in which a diagnosis is dependent on a quantitative score or count, such as estrogen receptor positivity or Ki67 count, require little skill but demand a disproportionate amount of a pathologist's time. If we can remove these mundane tasks from pathologists' workloads by using AI to make quantitative determinations from slide images, we will free up more time for crucial, highly skilled tasks that aren't easily replaceable by technology.

> *"The image analysis can run on a computer in the background and the pathologist can pull up the case when complete and instantly read the results."*

Another benefit comes in the form of time to diagnosis. The image analysis can run on a computer in the background and the pathologist can pull up the case when complete and instantly read the results. Increasing throughput in this way ultimately leads to more timely diagnoses for patients. AI can also help in terms of subspecialty staffing – when the technology can begin to help make

"AI systems are not sensitive to burnout, reducing the risk of human error that comes naturally from exhaustion."

diagnostic calls and triage cases for review by the pathologist, workloads will become more manageable and precious resources can be more efficiently directed.

But how do the benefits promised by AI translate to more accurate detection and better mitigation of diagnostic error? One of the strengths of AI is its ability to be implemented to detect and flag discrepancies. It's also well documented by now that the combination of doctor and AI is more accurate than either on its own. Therefore, a combination of both human and AI expert systems can reduce misclassifications and prevent the potentially harmful ramifications of misdiagnosis for the patient. In addition, AI systems are not sensitive to burnout, reducing the risk of human error that comes naturally from exhaustion. This, coupled with the fact that AI systems can complete tasks to a consistent standard regardless of location or time of day, makes AI an attractive prospect for addressing diagnostic errors.

A question of trust

It has already been shown that AI can perform as well as, or even better than, the pathologist – but this depends on the type of task undertaken. For example, if it's a binary call (such as the presence or absence of disease), pathologists can make that decision quickly and with high concordance between different individuals. If it's a more quantitative grading of disease severity or the crucial task of outcome prediction, the performance of AI has the opportunity to exceed that of the average pathologist in terms of speed and accuracy. In cases that demand a large amount of quantitation with high levels of consistency and accuracy, pathologists already begin to lose out to AI, simply because the human eye and brain have not evolved to score

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consistently and precisely over long periods. The more this type of task is needed, the more support AI can offer.

Given this great potential, it's fair to wonder why diagnosticians haven't yet fully embraced AI. The answer to that question lies in a uniquely human attribute: trust. Although there is a wealth of evidence that AI can perform specific image analysis tasks accurately, questions about safety and generalization remain. If we train an AI model on a patient population in Boston, will it work effectively on patients in Amsterdam? Pathologists have excellent localized knowledge and better risk awareness than AI systems; they can spot immediately when something appears odd or different to the norm. AI systems struggle to recognize when something is amiss – especially when we force them to make a call solely on the presented image.

There are also issues with patient demography, which occur if the composition of patient populations changes over time. Because it's impossible to validate AI systems against the entire human population, they can't address all demographic changes without human intervention. AI is still an emerging tool and, although we are very good at understanding where humans fail – and have systems in place to detect and reduce the impact of those failures – we are yet to fully appreciate the ways that AI can fall short.

Indirect impacts

There's only one way to further our understanding of the advantages and limitations of AI – and that's through widespread adoption of the technology in clinical research and, eventually, clinical diagnostic settings. Only then will we be able to obtain real-world, parallel evidence about AI's capabilities compared with those of humans. It's vital that this data comes from pathologists and not from stakeholders using AI for academic projects, which are not always reproducible, scalable, or transferable to patients. Only by using AI in a controlled and safe environment can pathologists begin to gather experience and expertise. As with all new technologies, early adopters will pave the way for everybody else.

However, it's important to assess the impact of AI in the correct way, especially as many of its benefits will be seen indirectly. AI systems might not improve health outcomes rapidly in the short term; although they will speed up certain tasks, that won't, in itself, necessarily improve diagnostic accuracy. Instead, it will free up time for the pathologist to carry out more complex, non-AI-based tasks that will impact health outcomes. The fact that such benefits are indirect consequences of AI assistance makes it difficult to quantify AI's involvement in the improvements to health outcomes.

To effectively measure the impact of AI, we will need to take a wide range of criteria into account: direct measurement of AI's performance, white paper economic analyses, and in-depth reviews of overall diagnosis rate. For example, do hospitals that adopt AI see – with the same staffing levels – an overall drop in problematic diagnoses? Do they see higher turnaround and better health outcomes than before the introduction of AI? It's a complex metric to assess, but there are ways it can be done.

AI's bright future

There's still a range of feelings among pathologists and laboratory medicine professionals toward AI in diagnostic medicine. Some people are staunch in their view that it's the doctor's responsibility to make the diagnosis (and not the computer's). I believe that is true, and that it will remain the case for a long time to come, regardless of new technology. Human disease is so complex that the fear of an AI system's taking over and replacing humans is hugely unrealistic. Physician burnout is much more of a concern than the takeover of AI and, until we are at the point where diagnosticians don't have enough work to do, it's more important to support pathologists with incredibly busy workloads in any way we can.

"There's still a range of feelings among pathologists and laboratory medicine professionals toward AI in diagnostic medicine."

The big question surrounding AI is not whether it can perform as well as humans; rather, it's whether AI systems can carry out tasks safely at large scales. Many non-health-based fields are ahead of pathology in terms of adopting AI but, in those cases, mistakes aren't as costly. In healthcare, even the smallest mistake can have serious consequences for patients – and that's why we have regulatory oversight on everything we do. The next hurdle for AI will be to prove that it can deliver safely across a large, variable patient population.

AI holds great promise for the future of medical diagnostics, especially when it comes to spotting and reducing diagnostic errors. Ultimately, both patients and pathologists will benefit from the widespread adoption of AI – and, thanks to faster time to diagnosis and safe, robust human-AI partnerships, diagnostic errors will hopefully become less prevalent.

Thomas Westerling-Bui is a Senior Scientist at Aiforia Inc, Boston, USA.

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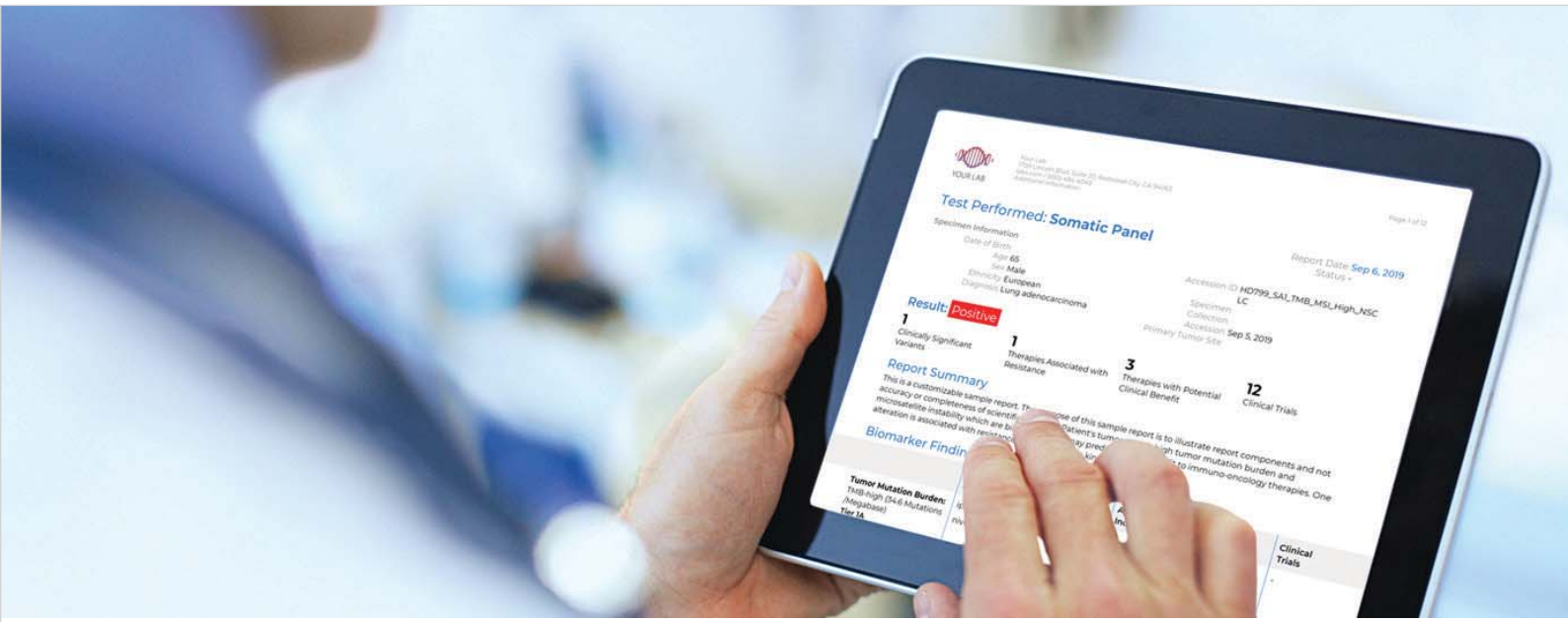

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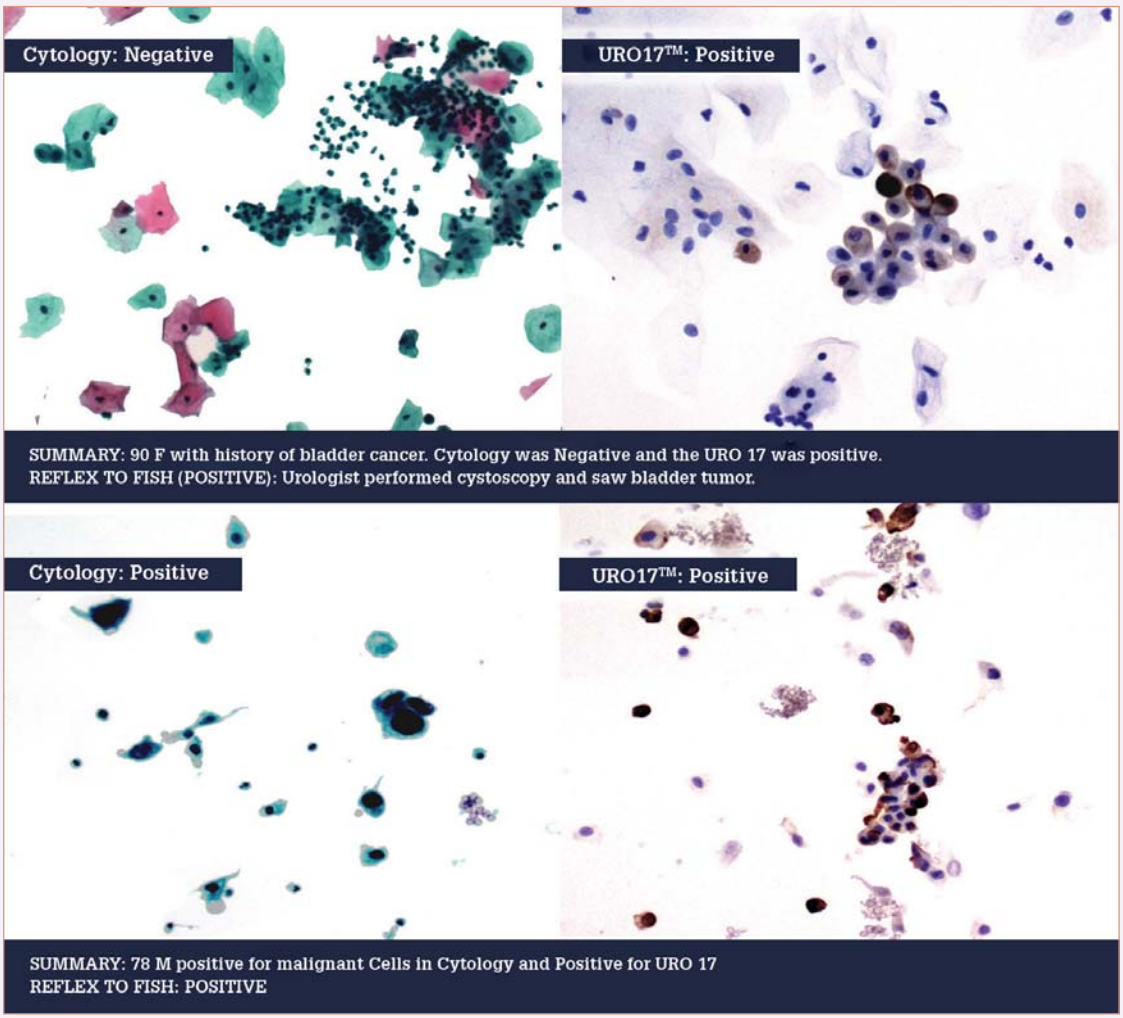

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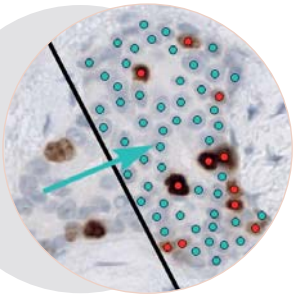

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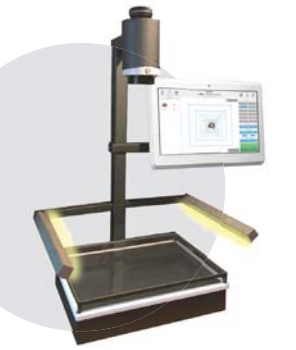

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Sitting Down With… Liron Pantanowitz, Professor of Pathology and Biomedical Informatics at the University of Pittsburgh and Vice Chair for Pathology Informatics at the University of Pittsburgh Medical Center, Pittsburgh, USA

How did your career begin?

Although I had always wanted to pursue a career in pathology, I found it to be the hardest subject at medical school. I presumed I would find something easier – but, after rotating through every other discipline, the spark had caught fire and I set my sights on becoming a pathologist. When I immigrated to the US from South Africa during my training, I noticed the stark difference in the levels of computerization and electronic records between the two countries. Despite great eagerness to use artificial intelligence (AI) in South Africa today, a lack of resources and vendors prevents computational pathology from taking hold. The distinct lack of pathologists – all of whom have high-volume workloads – makes it the perfect setting for AI to make a real difference, but they just don't have the capability to deploy it.

When I arrived in the US, I was immediately attracted to pathology informatics and, thanks to the mentorship of Bruce Beckwith, I was never afraid to try new technologies. Once I arrived at the University of Pittsburgh Medical Center, I had the perfect Petri dish in which to think big and grow the clinical potential of digital pathology and AI.

How will AI's impact be felt in the future?

There will be positives and negatives for everybody. On the one hand, I believe that AI will excite people and get them even more interested in their daily work. For trainees, it will be extremely intriguing to work with the technology that will shape the future of their field. I've involved trainees in the validation of several AI algorithms and many have subsequently written to me to express their enthusiasm. But there are fears that, because AI has the potential to take over much of the heavy lifting in pathology, it will leave people de-skilled.

At this stage, so few labs have experienced routine AI use that we just don't know its true impact yet. As we traverse this new and exciting landscape, it's important to be cautious and validate new algorithms thoroughly, ensuring that we keep a close eye on them. We also shouldn't make the assumption that AI will always lead to improvement. In a trial of a new algorithm that counts mitotic figures in breast cancer, we asked 27 users – ranging from second-year trainees to senior pathologists – to use the AI tool. Although the algorithm improved efficiency overall, five of the users were slower with AI and we have yet to understand why. We are heading into the unknown and there will inevitably be some failed deployments alongside the many success stories.

How can institutions gain from being early adopters of AI?

I'm a strong supporter of the partnership between academia and industry. In the drug world, the partnership between pharmaceutical companies and academic institutions results in a win-win-win situation: a win for the pharma industry, a win for the academic institution (by advancing science, improving their reputation, and increasing publication rate), and a win for the field in general. I see the same thing happening in pathology with the introduction of AI.

Early adopters will have the opportunity to work with AI start-ups and co-develop deep learning algorithms, whether by providing ideas for applications or supplying data for development. For algorithms that have already been built, institutions can provide the platform to integrate them into routine practice by testing whether they fit into existing workflows. But there are also indirect benefits to adopting AI. The reputation of institutions that adopt the technology is enhanced and noticed by patients, colleagues, and trainees alike – and trainees are increasingly attracted to institutions that can offer a digital pathology and AI platform.

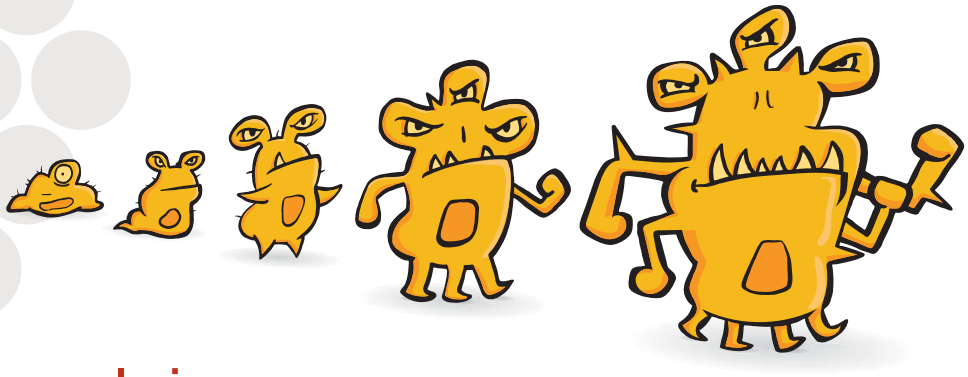
Most excitingly for me, I can now use AI to make new discoveries about disease, which is exactly why I became a pathologist. For example, we have an algorithm that can automatically screen urine cytology slides to make a diagnosis. Using it, I can now analyze close to two million cells and search for new disease patterns or correlations, which wouldn't have been possible manually. It's not all about performing mundane tasks when it comes to AI; rather, once these tools are at your disposal, you can start to run quality assurance on data and images while carrying out routine work. It's like having a new microscope in the lab!

What is your greatest personal achievement?

I founded the Journal of Pathology Informatics and, with the help of forward thinking colleagues including Anil Parwani and Mike Becich, the publication is now 10 years old, of which I am immensely proud. It was affiliated with the Association for Pathology Informatics (API) and provided a vehicle through which everyone involved in the field could share their research, whether or not it was successful. I think it has helped to shape the field of pathology informatics by bringing together pathologists, computer scientists, and clinicians to focus on a central theme. Consequently, I'm thrilled to have been selected for the API's 2019 Lifetime Achievement Award.

What are your biggest interests outside the lab?

I love music! I especially enjoy going to rock concerts and watching Broadway musicals, the latter being a common family outing. Unfortunately, I don't get enough time to play golf or read, but maybe AI will facilitate that!



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- *Staphylococcus*
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*
  - *Staphylococcus lugdunensis*
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  - *Streptococcus pneumoniae*
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DELL Technologies

Solution Brief | Digital pathology solutions from the slide to the data center to the cloud

Digital pathology—how next generation technologies are helping to generate critical insights from tissue samples

The convergence of advanced imaging, automation, and powerful analytics like natural language processing (NLP), machine learning, and artificial intelligence (AI) in healthcare and life sciences organizations are bringing together the tools needed for scientists and clinicians to unlock medical breakthroughs at a pace like never before. In emerging advanced imaging workloads, digital pathology is playing a central role by providing an extra layer of information augmenting the overall picture of an individual's distinct disease state.

With the aging population, healthcare providers have seen an increase in the prevalence of cancer and other diagnostic-intensive diseases amidst a global shortage of pathologists and laboratory services to provide diagnoses. Due to the accelerating growth in diagnostic information, health IT departments are being tasked with providing the infrastructure to digitize tissue sample slides.

Turning the slides into digital files enables pathologists to view, analyze, and manage these images with the use of technology. Electronically capturing tissue samples not only digitizes the images but also opens up a whole new world of opportunities, including:

- A means to augment the pathologist workforce gap through remote access and telepathology.
- A digital archive of the patient's sample rather than having to rely on preserving a slide or frozen section that requires physical space for storage, makes immediate peer consults challenging, and may be subject to degradation.
- A critical piece of the precision medicine puzzle. When combined with other disease-specific data like genomic profiles, digital pathology has the potential to improve the therapeutic benefit of treatment and lower or eradicate side effects on a per-patient basis.
- Advances in medical discoveries and diagnoses for "like patients"—for example, through access to anonymized data in support of large-scale cancer research trials and drug discovery.

The true value of digital pathology: leveraging data to create actionable insights

In order for digital pathology to empower precision medicine, augment the pathology workflow, and lead to medical advancements, significant data management challenges need to be addressed in a seamless way. These include:

Providing expandable storage: A single slide captured by a whole slide imaging (WSI) scanner can be 2-3 GB in size. Multiply that by hundreds of slides imaged per day, and it's clear to see why expandable capacity is required to maintain an ever-growing repository of historical image data.

Categorizing unstructured data: On its own, the digital image of a scan is not much more useful than the physical slide. For an image to have value, it needs to be ingested into a structured system—with fast access for collaborative purposes. This involves the creation of hundreds of annotated tags to go with the image, requiring high-performance computing power and AI-enhanced processing. This metadata, along with medical notes, must be combined with the digital images and placed together into object storage and attached to the patient's electronic medical record (EMR).

Offering anytime, anywhere access: Digital pathology image data and its tags need to be accessible both within the local healthcare facility and across the wider medical community for primary diagnosis, remote consults via telepathology, and virtual peer review for difficult-to-diagnose cases as well as for clinical trials, education, and research. When these images are not stored in a silo but are integrated with a laboratory information system (LIS), an EMR, and other systems, this approach ensures data portability for a complete patient view.

The benefits of digital pathology are maximized when this integrated data architecture is combined with high-performance computing, fast servers, flexible scale-out network storage, and direct, secure access to a multi-cloud environment with big data analytics capabilities. Dell Technologies, leveraging our partner ecosystem, plays a central role in providing an interoperable network for digital pathology.

End-to-end solutions to streamline digital pathology

Dell Technologies offers a portfolio of solutions that span the entire digital pathology IT environment from high-performance compute and high-resolution displays to servers, networking, storage, and software to multi-cloud and big data analytics platforms. Our digital pathology solutions include:

- **Flexible, scalable storage for big data:** Dell EMC Isilon—the industry's #1 family of scale-out network-attached storage systems—and Dell EMC ECS Object Storage provide the high performance and scalability options needed to grow dynamically as imaging data is supplied by WSI scanners. A full range of options are available and work with your multi-cloud environment or on premises—from all-flash devices for extreme performance to lower-cost archival solutions as well as object-storage platforms able to manage unstructured data at exabyte scales. Dell Technologies provides solutions that enable pathology data stored on an Isilon platform to be located, provisioned, and executed quickly, with the ability to identify specific data sets by any number of parameters such as patient name, disease type, date, or unique patient identifier—from anywhere across the globe.
- **High-performance compute for fast data indexing:** Dell EMC PowerEdge servers offer enhanced performance across the widest range of applications to accelerate the indexing of large WSI datasets for fast retrieval, including Dell EMC VxFlex hyper-converged infrastructure (HCI) and appliance-ready options. Dell EMC's comprehensive High Performance Computing (HPC) Solutions, including NVIDIA GPU- and Intel FPGA-accelerated servers, deliver specialized processors and accelerators for intensive precision medicine workloads such as AI-enabled drug discovery.
- **Advanced analytics for meaningful insights:** Choose a Dell Technologies solution that's right for where you are on your data analytics journey. Dell EMC Elastic Data Platform provides a basis for data analytics while Dell EMC Ready Solutions for Data Analytics in healthcare help you unlock the value that exists within your pathology and other medical data.
- **Modern infrastructure for quick, secure data access:** Dell EMC VxBlock System Converged Infrastructure simplifies the infrastructure needed to access and run WSI applications with turnkey, fully integrated storage, data protection, servers, and virtualized networking functions for today's software-defined data center (SDDC).
- **Multi-cloud integration for collaboration:** Accelerate your multi-cloud journey as you deploy applications and indexed WSI data in the right cloud—whether in a private cloud that is fully under your control or a public cloud or at the edge. Dell Technologies Cloud powered by VMware seamlessly extends from the public cloud into your data center to deliver a simpler cloud experience. Together with our robust cloud partner network, we enable consistent hybrid cloud operations, reducing the complexity of managing multiple clouds.
- **High-definition displays for enhanced viewing:** View images in extraordinary detail using a display from Barco Medical Imaging Solutions. Dell Large Format Monitors are also a great fit for onsite collaboration or teaching purposes.

Advancing digital pathology with Dell Technologies Solutions
Modern infrastructure from Dell Technologies helps facilitate digital pathology applications by providing critical solutions and partnerships to turn data into insights at every stage of the digital pathology workflow (Figure 1). From the slide to the data center to the cloud, our offerings enable pathologists, researchers, and healthcare systems to ingest and analyze data in real time; provide meaningful, actionable insights; retain data for deeper analysis; and seamlessly share data with collaborators, patients, payers, and healthcare and life sciences organizations to improve outcomes.

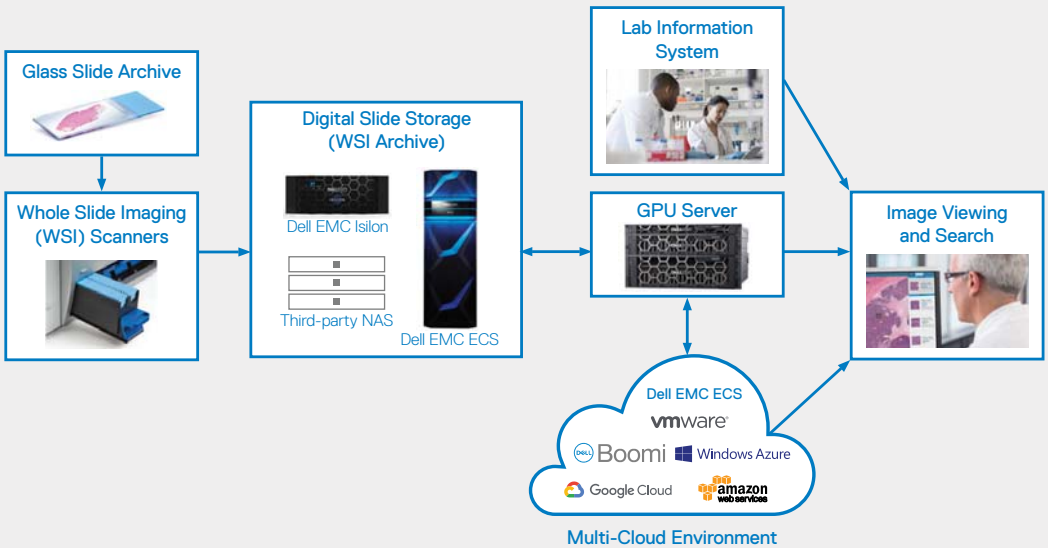

Figure 1. Reference architecture enabled by Dell Technologies—a ready bundle for your digital pathology workflow including high-throughput scanning, real-time indexing, and secure, managed access to digital slide repository and pathology reports inside and outside the organization

Learn more about our solutions for healthcare

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