NOVEMBER 2016 # 24

the Pathologist

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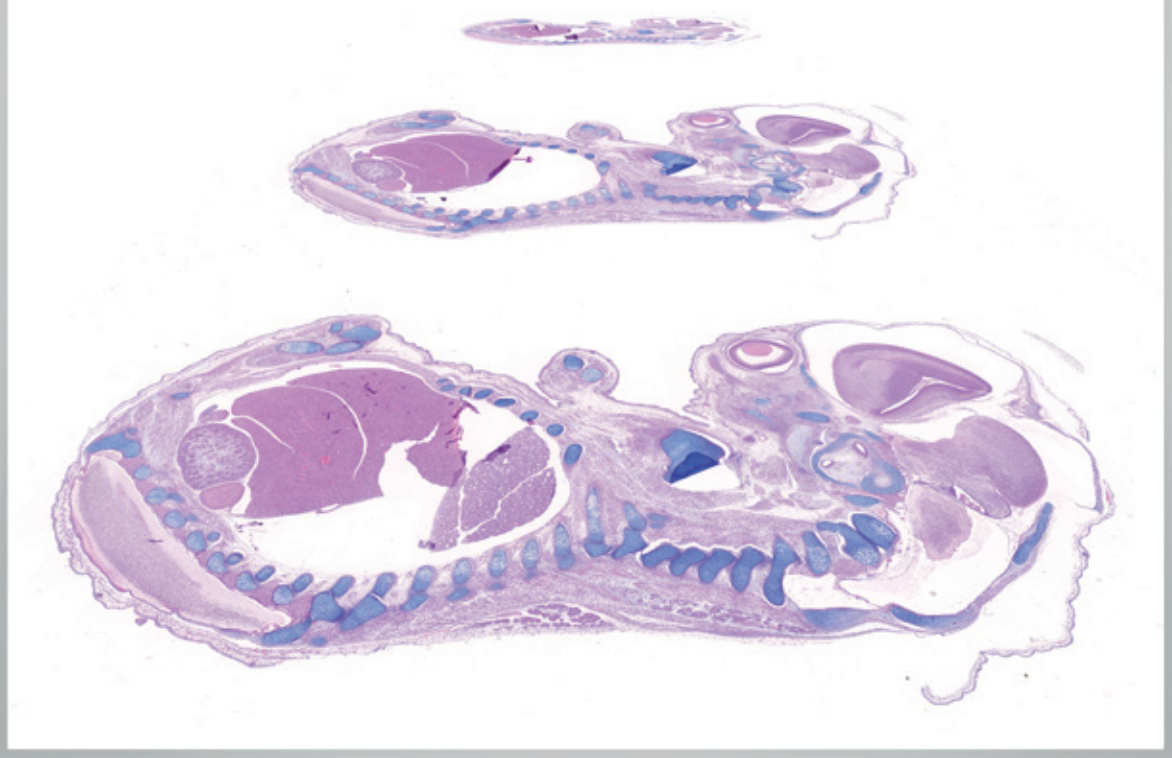
Image of the Month



This sagittal section of a fetal degu at 60 days of gestation is stained with hematoxylin and eosin and Alcian blue. The developmental state of the brain, eyeball and inner ear can be seen in the lower right, along with cartilaginous plates in the spine that form the ribs and limbs. In the fetus' abdomen, the liver and lungs clearly show an advanced stage of development. The veterinary pathology image was captured on a NanoZoomer-XR digital slide scanner at 40X by Cleo Bosco of the Centro de Patología Digital Asistido por Internet, Faculty of Medicine, University of Chile.

Do you have an image you'd like to see featured in The Pathologist?
Contact fedra.pavlou@texerepublishing.com

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No Sympathy, No Humanity

When public health disaster strikes, the lab heroes step in

I had the privilege of being invited to moderate a session at a very special event hosted by the Royal College of Pathologists earlier this month. Held in London, this was by no means a UK-centric event; "Pathology is Global" aimed to highlight the role of pathology and lab medicine in humanitarian disasters and public health emergencies and it did so in a captivating, thought-provoking, emotional, inspiring way.

"I'm happy to be here and I'm happy to be alive," was Sahr Gevao's poignant opening sentence. Heading up lab services in Sierra Leone during the Ebola outbreak, Gevao witnessed the tragic death of many of his colleagues, and though his account was filled with sad stories and shocking statistics, he delivered his presentation with pride. Because, in spite of the dire geographic infrastructure, and the paucity of labs, staff, equipment and facilities, the dedication and compassion of the people that he worked with led to many lives saved, even though their own were at high risk. And what I found heartening was Gevao's commitment to helping others who may find themselves in similar situations – based on his own harrowing experience, he gave recommendations on what could be done to help save lives quicker.

As tough as I'm sure it was for Gevao to relive those memories, his presentation followed that of Professor Amy Patterson, who gave a no holds barred account of the international response (or lack thereof) to public health emergencies. In a nutshell, if you're not able to generate the sympathy vote with the media or you're seen to be culpable in any way for a health emergency, you fall down on the priority list for international response. In the case of Ebola, Patterson flashed up images from US press of an African man holding a bat, with the article suggesting bush meat was the source of Ebola and hence responsibility lay with the relevant communities for the spread. "Perception is so important to organizations and policymakers," she said. According to her, it wasn't until Ebola appeared to be an international threat, and one that the West wasn't immune to, that a full-scale international response was triggered. Please don't assume that Patterson was very matter-of-fact about this; she was, I sensed, impassioned and angry. Imagine how Gevao felt? And his wasn't the only heart-rending story of the day.

This was one of the best events that I have attended and I'm honored to have shared a room with some truly inspirational people. I really hope to be able to do some of these stories justice in future issues of The Pathologist. Watch this space, but in the meantime, take a look at some of our social media coverage of the event (1).

Fedra Pavlou
Editor

Reference

1. *https://storify.com/pathologistmag/pathology-is-global*

Danny Milner, Jr.

Danny is the Chief Medical Officer of the American Society for Clinical Pathology (ASCP) and Director of the ASCP Center for Global Health. He has worked on research, clinical service, and humanitarian projects in Africa since 1997, is involved in research, clinical, and humanitarian projects in Mali, The Gambia, Uganda, Mozambique, Zambia, Madagascar, Sri Lanka, and Haiti, and his current global health efforts are focused on AIDS relief and rapid cancer diagnostics using telepathology.

Claire Wagner

Previously a research fellow to Rwanda's Minister of Health, Claire is now a Union for International Cancer Control Fellow supported by the US National Cancer Institute Center for Global Health. She is also Senior Consultant to the Dana-Farber Cancer Institute Center for Global Cancer Medicine.

Lawrence Shulman

Larry is Deputy Director for Clinical Services at the University of Pennsylvania's Abramson Cancer Center and Director of their newly formed Center for Global Cancer Medicine. He also works with the cancer program in Botswana and serves as Senior Oncology Advisor to Partners In Health (PIH), supporting the establishment of national cancer treatment programs with the Ministries of Health in Rwanda and Haiti.

Danny, Claire and Larry provide their thoughts on cancer diagnostics in developing countries and call for urgent action from the international community on page 14.

Liron Pantanowitz

Liron is Director of Pathology Informatics and the Pathology Informatics Fellowship Program at the University of Pittsburgh Medical Center, Past President of the Association of Pathology Informatics, and a leader in the College of American Pathology and Digital Pathology Association. He is Editor-in-Chief of the Journal of Pathology Informatics and widely published in the field of digital pathology. "Innovating in informatics pushes the limits of our discipline," he says. "As a result, I have come to expect the unexpected."

Turn to page 29 for Liron's thoughts on building a digital pathology business case.

Luke Perkocha

Luke Perkocha practices anatomic and clinical pathology, with a subspecialty in dermatopathology, at Kaiser-Permanente in Northern California. He has a degree in business administration and writes and speaks about business and technology/informatics topics in pathology and laboratory medicine. "It's prudent to be constantly scanning for 'killer apps' or environmental changes that can upend the traditional practice of pathology," he says, "but it's important not to be overly wowed by technology for its own sake."

Hear Luke's position on digital pathology's return on investment on page 20.

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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?

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Tackling the Ticking Treatment Clock

Genomic and proteomic testing at the point of diagnosis can speed up treatment decisions for cancer patients

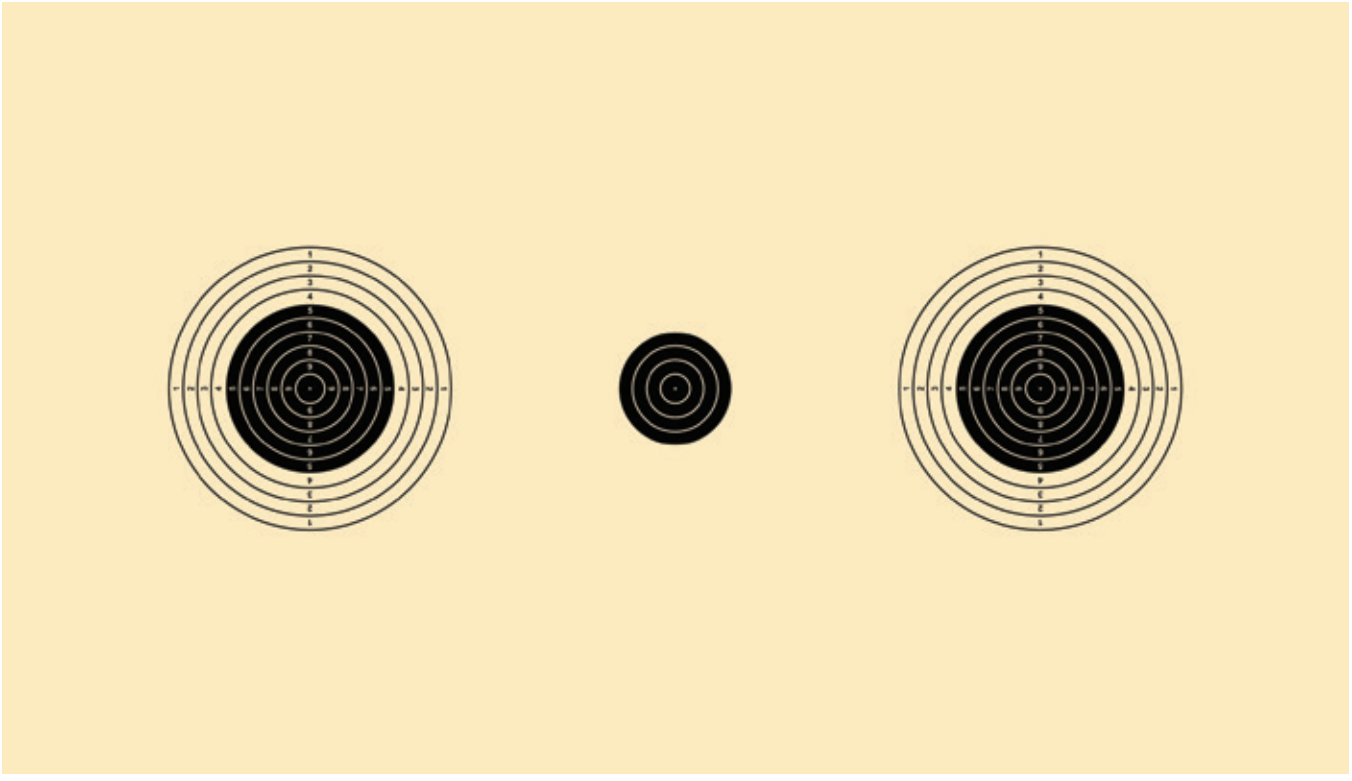
Pathologists know that the longer a diagnosis takes, the more difficult it may be to treat disease. That's why so many improvement efforts include words like "speed," "efficiency" or "turnaround time." But if you're really seeking new ways to improve, one option to consider is introducing personalized medicine at the point of diagnosis. If a simple blood test can point the way to effective treatments and prevent time wasted on those that won't work, why not perform it as soon as possible?

Results from a Wisconsin-based group's recent study on blood-based genomics and proteomics in lung cancer indicate that such tests can significantly shorten the time newly diagnosed patients spend waiting for treatment (1). It's especially relevant because non-small cell lung cancer (NSCLC) is often detected in its advanced stages, when delays can have a significant impact on treatment outcomes. Genomic and proteomic testing can reveal specific mutations that may make tumors sensitive – or resistant – to particular treatments. Not only that, but they can provide the information within 72 hours of the blood draw, much faster than performing similar tests on biopsy samples. In the study's sample population, the 21 percent of patients who had genomic testing at diagnosis had shorter times from consultation to treatment decision (0 days, compared with 22 days in patients who were untested) and treatment start (16 days, compared with 29 days in untested patients). Regardless of disease stage, genomic testing provided patients and physicians with vital information for treatment selection and prognosis.

With diseases like NSCLC, where every day counts, perhaps these rapid and revealing blood tests are the way of the future. *MS*

Reference

1. *J Mattingley, K Oettel, "Blood-based genomic and proteomic testing for newly diagnosed lung cancer patients to facilitate rapid treatment decisions and prognostic conversations", Chest, 150, 721A (2016).*



A Personal(ized) Choice

Does precision medicine really make a difference in cancer care? Results of a recent study say it does

Precision medicine grabs a lot of headlines these days – new tests, new diseases, and new ways of personalizing treatment to individual patients. But with therapies and technologies advancing daily, sometimes it's hard to see the wood for the trees. The University of Michigan School of Nursing's Christopher Friese asked a simple question often overlooked: "Is precision medicine actually helping?"

Fortunately for the 1,527 patients he surveyed – and countless more who receive genetic and genomic testing to help guide treatment decisions – the answer seems to be yes (1). Friese asked women diagnosed with early-stage breast cancer two questions: whether or not they had received the 21-gene recurrence score assay, which assesses a patient's likelihood of relapse; and whether or not they had received chemotherapy. Current guidelines recommend the test for certain patients (those with particular tumor features and no spread of disease to the lymph nodes). A high score on the test indicates a need for chemotherapy. Ultimately, Friese and his colleagues found that most doctors' testing recommendations were in line with the guidelines, and that the assay correlated well with treatment decisions. 87 percent of women with a high recurrence score (RS) received chemotherapy, whereas only 3 percent of those with a low RS did. Notably, 13 percent of women with no RS but a favorable prognosis were given chemotherapy – meaning that the assay may substantially reduce overtreatment.

Although it seems doctors are using precision medicine well and satisfying patients (with most agreeing that the test was helpful and that they were happy with their treatment), Friese did note one area for improvement. Only 60 percent of patients accurately recalled their test results – which Friese believes could be remedied if both the assay and the outcome were better explained. Personalized treatment may be complicated, but it's one more opportunity for pathologists to speak up and explain to patients the science behind their care. *MS*

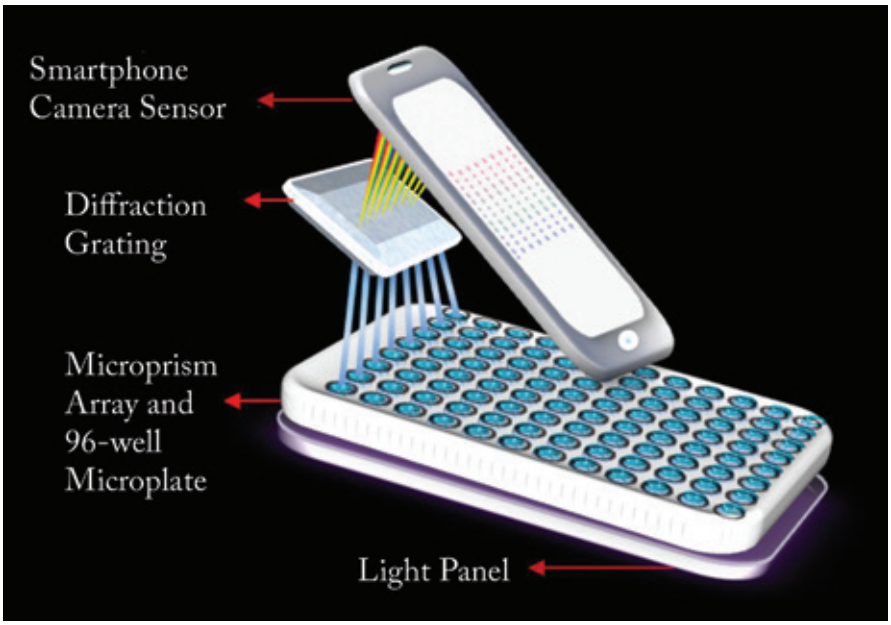
Reference

1. *CR Friese et al., "Chemotherapy decisions and patient experience with the recurrence score assay for early-stage breast cancer", Cancer, [Epub ahead of print] (2016). PMID: 27775837.*

Tiny Testing

A new device allows pathologists to look for cancer biomarkers in eight samples at once – affordably, accurately, and on a smartphone

In the hunt for better diagnostics, the game is always afoot. We want them fast, cheap, accurate and portable – attributes that aren't always easy to combine into a single device. But now, a group of researchers think they may have cracked the code with a new "smartphone laboratory" (1) designed to detect the cancer biomarker interleukin-6 (IL-6).



Credit: Washington State University.

A diagram of the smartphone laboratory in action.

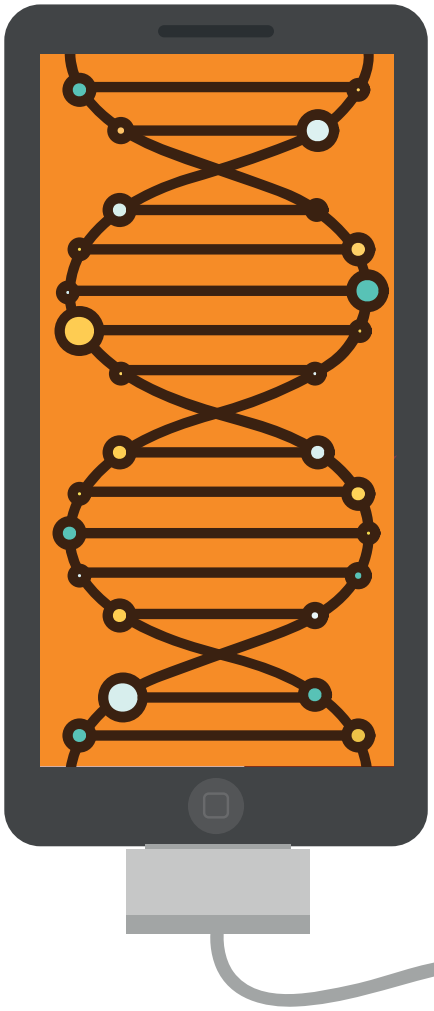
Who?
A Washington State University research group in the School of Mechanical and Materials Engineering. The project is led by Lei Li, an assistant professor with an interest in diagnostics and precision engineering.

What?
A portable, eight-channel spectrometer that works with an iPhone 5. By using 3D-printed accessories and a newly developed manufacturing process, the researchers were able to bring the cost of the device down to less than US$150.

Why?
Current smartphone spectrometers are single-channel, meaning that they can only analyze one sample at a time. That makes them slow if multiple samples are tested, or risks decreasing accuracy if users examine only one or a few samples. Running eight samples at once allows the WSU scientists' device to not only work more efficiently, but also deliver results with up to 99 percent accuracy – as good as laboratory-based tests. This is especially useful for pathologists working in remote or resource-limited settings, where full laboratory setups may not be available.

How?
The spectrometer runs ELISA tests, using spectrometry to measure the change in color as antibodies in the assay react to IL-6 in the samples. IL-6 is a known biomarker for numerous cancers, including lung, liver, breast, prostate and epithelial – so its presence in a sample indicates a potential malignant tumor.

What next?
Li is working on a newer version of the device that can be adjusted to work with any model of smartphone. In the meantime, he and his colleagues are testing the existing device in real-world situations to see how it might perform in the field. *MS*



Reference

1. *LJ Wang et al., "A multichannel smartphone optical biosensor for high-throughput point-of-care diagnostics", Biosens Bioelectron, 87, 686–692 (2016). PMID: 27631683.*

The Shape of Things

Could cancer cells' shape help pathologists predict their behavior?

It's not unheard-of to use a cell's shape to inform a diagnosis. The classical example is sickle cell disease, where the red blood cells have an unusual, crescent-like shape, but other such disorders exist. What if we could use cell shape to not only detect disease, but also predict its course? That's the question Elaheh Alizadeh, Ashok Prasad and their colleagues took on in their recent paper on the shapes of cancer cells (1).

We already know that the disease process of cancer involves misregulation of the cytoskeleton, which leads to cell deformity. What Alizadeh and Prasad hypothesized is that, before such changes become visible to a pathologist at the microscope, there may be much smaller, subtler changes detectable only with the aid of a computer. To decipher these potential changes, they selected a set of 256 individual cell shapes and characterized each one – and the differences between them – mathematically. Next, they used four known osteosarcoma cell lines with varying degrees of invasiveness to teach a computer to distinguish between different degrees of aggression based on shape. Only once the computer was fully trained did they expose it to a hypothetical fifth cell line – and discovered that it accurately predicted the invasiveness of the new cells.

What's next? A lot more work. The scientists need to examine better ways of preparing cells for imaging so that their shape is not impacted, as well as exploring new methods of evaluating and quantifying cell shape. Once the method is refined to the point where it can reliably be used to link shape with potential prognosis, might it give pathologists another perspective on disease. *MS*

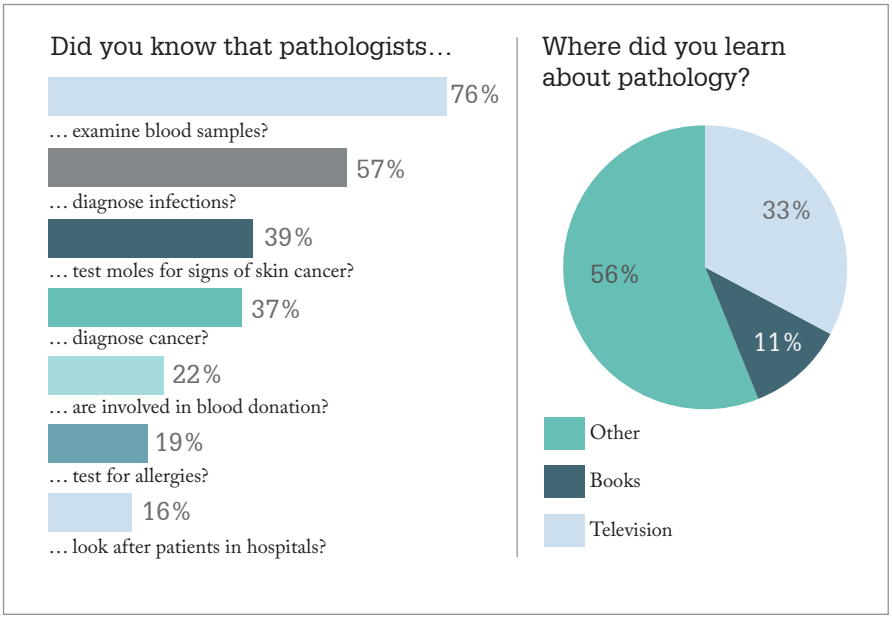
Reference

1. *E Alizadeh et al., "Measuring systematic changes in invasive cancer cell shape using Zernike moments", Integr Biol (Camb), 8, 1183–1193 (2016). PMID: 27735002.*

Mythbusting Medicine

The general public's understanding of pathology is still low – so perhaps it's time to step up awareness initiatives

The Royal College of Pathologists recently surveyed over 2,000 adults in the United Kingdom to find out what they knew about pathology. What did they find? It's a bit of a mixed bag. For instance, while over three-quarters of respondents knew that pathologists were responsible for analyzing blood samples, not even one in five knew that they diagnosed allergies or looked after hospitalized patients. Most were aware of fictional pathologists – but unfortunately, that meant that their understanding of pathology was largely limited to forensic science, a discipline in which less than 1 percent of pathologists specialize. The take-home message? That pathologists need to encourage better public awareness of the work they do, so that patients can fully understand the roles of every member of their healthcare teams. *MS*



Key findings of recent survey of the Royal College of Pathologists on public awareness of pathology.

Reference

1. *S Jayaram, "Fact or fiction? Royal College of Pathologists public survey finds mixed attitudes to pathology" (2016). Available at: http://bit.ly/2fv124I. Accessed November 12, 2016.*

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 editor at fedra.pavlou@texerepublishing.com

Pathology is a Human Right

Battling the ever-growing burden of cancer in Africa requires a global effort

By Danny Milner, Jr., Chief Medical Officer of the ASCP and Director of the ASCP Center for Global Health; Claire Wagner, Union for International Cancer Control Fellow supported by the US National Cancer Institute Center for Global Health, and Senior Consultant to Dana-Farber Cancer Institute Center for Global Cancer Medicine; and Lawrence Shulman, Deputy Director for Clinical Services of the Abramson Cancer Center at the University of Pennsylvania

Infectious disease remains a major challenge in low- and middle-income countries (LMIC); however, political will and global funding mechanisms over the past two decades have resulted in the widespread rollout of advanced diagnostic capacity and drug delivery, especially for HIV/AIDS, tuberculosis, and malaria. Although the problem of cancer existed long before – and mortality from these infectious diseases is reduced – incidence of malignancy and other non-communicable diseases have risen as a proportion of overall disease burden. Moreover, with better control of infectious disease, the populations of all countries are aging, adding to the increase in cancer burden. Policy makers and other public officials are now recognizing more than ever the urgent need to address cancer.

Unlike HIV/AIDS, tuberculosis, and malaria, cancer comprises many heterogeneous diseases and is more complex to diagnose and treat. For example, a highly effective and potentially curative treatment for Hodgkin's lymphoma will be completely ineffectual in a patient with colon cancer. Therefore, without a specific diagnosis, optimal therapy cannot be determined, and poor outcomes are likely to result. Also, as we know, cancers cannot be definitively diagnosed clinically and require histologic evaluation of biopsied material; so, the pathologist and his/her laboratory play an essential role in cancer care. Likewise, without access to safe and effective therapies, an accurate diagnosis of a patient with cancer is a hollow effort. The patient may know what disease they have but will still die without the appropriate treatment. It is clear that diagnosis and treatment must go hand in hand.

Diagnosing cancer requires, in the traditional workflow, a series of personnel (pathologist included), instruments, and reagents that are expensive and difficult to maintain in harsh environments. Under these challenging conditions, most pathology facilities in LMICs would be deemed limited in both resources and capacity. Further, the evaluations of tissue that are required for responsible patient care go beyond accurate histologic diagnoses. Doctors also need additional tumor-specific data to design a treatment regimen aimed at maximizing the likelihood of survival for the patient (for example, estrogen receptor and HER2 status for breast cancer, or the presence of the t(9;22) chromosomal translocation in chronic myeloid leukemia).

Providing high-quality pathology services is already a formidable task in wealthy countries such as the USA and very much more so in LMICs. Pathologists in any context must be well trained, and, as is the case with all physicians, continuing medical education focusing on new developments and technologies is essential. Working within a peer group and scientific

community that provides consultation and support is also critical regardless of the setting. Pathology labs have universal requirements too – for instance, they need the necessary equipment, numerous and inter-dependent reagents, and skilled technicians to process specimens. Machinery must be maintained in excellent functional status and promptly repaired when rendered non-functional. Consumables (including reagents used) must be kept in stock, which means supply chains must be tightly run. The absence of one critical functional machine or reagent will often bring the lab to a grinding halt – the "weak link in the chain" phenomenon. A pathologist without a high-quality laboratory is ineffectual, as is a functioning laboratory without a pathologist.

In many countries in sub-Saharan Africa, and other impoverished regions of the world, there are few if any pathologists. The needs of their lab's catchment area (sometimes their entire country) and the volume of specimens that need processing, often hugely overwhelm those pathologists who are running labs. There is often little support available to pathologists in processing specimens, producing reports, and assuring the reports get back to the treating physicians. Even if the number of pathologists in training is increasing, there will still be a vast shortage of pathologists for many decades to come.

In these settings, high quality cancer care is extremely challenging but not impossible. One way that organizations have tackled human resource shortages and weak pathology infrastructure is through global partnerships with academic medical centers in the United States and elsewhere. We have learned that the establishment and maintenance of high-quality pathology in these settings is feasible and can benefit tremendously from support of pathology colleagues from cancer centers with comparatively abundant resources.

Such long-term partnerships can act as a buffer to the drawbacks of one-off pathology training courses that, although essential, are often inadequate for programs to remain sustainable. Ongoing engagement can make the difference between a sustainable program and one that collapses under the weight of unmanageable volume of specimens and other challenges. Accompaniment often takes the form of on-the-ground support by pathologists and technicians, as well as long-term support through telepathology. In all circumstances, continual quality assessment and improvement, as well as peer support through a scientific community, can help guarantee excellence.

Many cancers are curable and many are controllable for years and even decades. Millions of patients worldwide with such cancers – like early stage breast cancer in a young woman, or chronic myeloid leukemia – die needlessly every year because they lack access to high-quality cancer diagnostics and treatment. One would hope that a four-year old boy with Wilms' tumor, who has an 80 percent chance for cure in the US, would not be allowed to die without even a diagnosis, no less treatment. Yet that happens every day in many places in the world. We have a humanitarian obligation to work to provide that child with a chance for cure – a chance for life – with safe and effective therapy. The first step is the capacity to make an accurate diagnosis, and therefore high-quality pathology is part of the human right to health.

We Must Guide POCT

Why it's important to establish ground rules and quality for point-of-care testing

By Xavier Navarro, Area Manager and POCT Coordinator, Laboratori de Referència de Catalunya. Barcelona, Spain

Point-of-care testing (POCT) should not be a new topic for laboratory medicine discussions but in some institutions, it is. And, those who are unaware of the potential problems of poor global quality management of POCT need reminding about it regularly, particularly as people who are not laboratory medicine specialists may perform the measurements!

Clearly, there are very good reasons for using POCT. For example, it reduces turnaround time (TAT) or "vein to brain time" (time from result availability to action taken), and it is advantageous in reducing unnecessary blood drawing (in intensive care and neonatal intensive care units). It also minimizes handling or transporting samples to the laboratory, improves patient care by reducing hospital visits and, therefore, unnecessary journeys.

I would say that, above all, any decision to implement POCT should be guided by a desire to improve patient care, eliminate problems caused because the laboratory cannot improve TAT, and overcome problems experienced with laboratory processes that prove difficult or impossible to improve. But, it is important to ensure that the quality of POCT is of the same high standard as those tests performed in the laboratory.

In my view, laboratory professionals should see POCT as an extension to lab work and subject it to the same quality standards. Consequently, there is no need to reinvent the wheel, just use your established

standards. Here are some of the basic items we have implemented within our POCT quality standards in Barcelona:

- take care of the patient
- create and lead a team
- analyze, simplify and document all processes
- select and evaluate POCT analyzers
- assure global POCT quality
- learn from errors allowing continuous quality improvement.

All of the above are simply what we've been doing for a long time!

Undoubtedly, every new POCT scenario should be developed with the aim of improving healthcare and patient benefits while maintaining outstanding reliability of every point-of-care measurement. Far from facing these tasks as individuals, it needs a strong team led by an experienced laboratory professional as POCT coordinator. I suggest that the POCT coordinator has very important responsibilities, including:

- selecting and leading a team of trained and strategic professionals
- deciding which global quality assurance protocols will be applied. He or she will monitor internal quality control, external quality assurance, process performance indicators, quality system assessments, and implement further improvements as necessary
- assuring access to important information allowing efficient and effective use of systems. He or she will demonstrate a deep knowledge of every test procedure (identification and preparation of patient, how to obtain and manage samples, analytical process, validation, etc.)
- establishing training plans for personnel (subjects, timing, assessment of acquired knowledge, etc.)
- assuring that all testing conforms to legal requirements.

Hopefully, your team will be multiskilled, comprising a variety of professionals from both healthcare (nurses, physicians, clinical laboratorians) and from other disciplines too (such as information technology, administration, and others). This will provide a unique opportunity to approach POCT subjects from several inspiring points of view.

In that context, clinical laboratory professionals will have a vital role in POCT team education and training by providing well-structured and easily understandable documentation and instructions for using POCT devices. This kind of education is necessary because there is a general lack of laboratory specific education for healthcare professionals, as well as a false assumption of "simplicity" of POCT devices, and an incorrect, general belief that whatever value obtained from a measuring system is true. So, laboratory professionals must publish clear, visual, and easy to read operating instructions. These must be available at the POCT site, allowing others to use POCT devices safely, with the highest quality throughout the measuring process, which will ensure reliable results, avoid errors and help protect patient safety.

Clearly, the participation of laboratory professionals in selecting and evaluating POCT devices will help to ensure that hardware is fit for purpose. Importantly, device evaluation must be to Clinical and Laboratory Standards Institute (CLSI) guidelines – this is mandatory, and so is observing global quality assurance regulations such as ISO9001, ISO15189, ISO22870 or any others (CAP, Joint Commission, etc). Finally, a well-structured quality assessment system is essential to enable continuous improvement and to contribute to patient safety.

By following the above and applying global quality standards here in Barcelona, we're achieving great things with POCT – and those are the same standards we've always used as laboratory medicine professionals.

Lessons in Life

Teaching pathology needs to be practical, dynamic, and inclusive. Students gain a lot more through learning the role of pathologist first hand. Here's why

By Sandra Zekic Tomas, staff pathologist, Split University Hospital; senior teaching assistant, School of Medicine, University of Split, Croatia.

As a medical student, I decided that studying pathology would be my first choice in preparation for my future career. Let's just say I fell in love with it at first, second, and every other sight. And, now my enthusiasm for teaching pathology continues my love story with the subject and field.

As well as being a practicing pathologist, I am also a senior teaching assistant in the associated medical school. I teach pathology and several other courses, such as medical studies, through the medium of English, dental pathology, pharmacy and nursing. In total, our teaching faculty has more than 800 scheduled student contact hours in the form of lectures, seminars, discussion groups, and practical laboratory studies.

Although I do not take myself too seriously, I am serious about my teaching assignments. I take time to prepare good

lectures and seminars, I read extensively, and I try to be as positive as possible to stimulate the students to participate in all the teaching sessions. I don't just want to explain various diseases from a pathological point of view, I also want to give the students an insight into the wonderful world of pathology, explain what a pathologist does in practice and how we make complex diagnoses just by looking at a gross specimen or microscopic slide. Imparting knowledge to my students is an enjoyable and rewarding venture!

"The facts speak for themselves because, year on year, the students have voted pathology as the best course in the medical curriculum."

Over the last few years, I've noticed that my colleagues from other universities are complaining about the diminishing status of pathology within the medical curriculum. Many of them claim that pathology is being pushed aside by other courses or that it is simply integrated with other basic or clinical sciences such as anatomy, physiology, internal medicine, or surgery. Fortunately, that's not our experience in Split, where pathology is taught as a self-contained, three-month module within the third year. During the three months, the students live and breathe pathology, spending their days with us in the lecture, seminar, microscopy, and autopsy rooms.

We treat the students as colleagues, welcoming them to our conferences and meetings, and they partake in the same tasks and daily obligations as the teaching faculty. The students love it and their course evaluations show that they appreciate our attempts to teach them pathology by playing the role of a real pathologist. The facts speak for themselves because, year on year, the students have voted pathology as the best course in the medical curriculum. Also, my colleagues and I have received numerous students' choice awards, which is further proof that our approach to teaching works.

We aim to teach students basic pathology and to introduce them to the study of various diseases from an anatomic and a pathophysiological point of view, with a strong emphasis on clinical-pathologic correlations. I find that the hardest part of teaching any subject is finding the right balance between the amount of information you want to give the students and the amount of information that is necessary for their further studies. I always ask myself how much "real" pathology should students know? Should they be able to tell the difference between malignant and benign cells under the microscope, recognize basic macroscopic changes in organs or attend autopsies? My answer is yes to all of these! I truly believe there is no better way to explain various diseases than by involving the students in the actual events that led to the outcome. So, our students attend autopsies (at least once a week), and this attendance is considered to be a required part of the pathology course. Before each autopsy, we discuss the patient's medical history, clinical signs, and symptoms, and predict possible macroscopic and microscopic autopsy findings. During the actual autopsy, the students are allowed to assist. This gives them a complete insight into a patient's case from the clinician's to the pathologist's point of view. I don't think that there is a better way to learn! Likewise, during the course, students are given a tour of the Pathology Department. We explain and show them what the pathologist actually does, teaching them how to perform frozen sections, dictate the gross and microscopic findings, and formulate the final diagnosis and medical opinion. Our students expect to be taken seriously in their studies, they enjoy active participation, and they assure us that they learn much more than just from reading books. These various activities enhance the quality of the course, which helps the students to understand the subject better, and gives them a clear insight to what we do on a daily basis.

Therefore, I believe it is crucial to teach students by including them in our daily activities, and treat them as partners, keeping all communication channels open, and forming a unified teaching/learning team. That way they will be ready to step into the shoes of qualified doctors, understanding the need to cooperate with colleagues and acting in the best interests of the patients.

I hope that I have convinced you that I truly believe in our full immersion, all-inclusive practice-based, teaching system of pathology. The system has worked well for more than 15 years to the acclaim of generations of medical students and without any burnout among the faculty. Perhaps, our approach would not work at a bigger university with hundreds of students and understaffed faculties, but it seems to be ideal for our small faculty of 20 pathologists, teaching 90 medical students a year.

I'll leave you with the valuable advice given to me by my own professor, Ivan Damjanov (Department of Pathology & Laboratory Medicine, KU Medical Centre, The University of Kansas, USA). He told me before my very first lecture, "Sandra you have to make the students laugh, if they aren't happy when they leave your class you're not doing it right!" I am glad to report that so far, my students are laughing and they seem to be happy.

Has Its Worth Been Proven Yet?

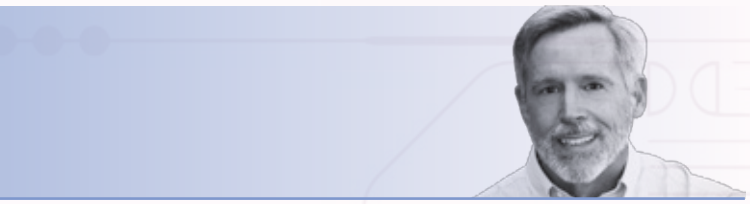
It's clear that the use of digital pathology technology is on the up, but what's less clear is whether or not there's a strong business case for it.

Digital pathology is making headline after headline as increasing numbers of laboratories adopt new technologies. But is it really saving them money? Five experts provide their views on the business case for digital pathology, and whether or not they think the transition is a worthwhile investment at this point in its evolution.

The Doubting Dollar

With the introduction of whole slide imaging (WSI) over a decade ago, "digital pathology" burst onto the scene with much fanfare, yet has had relatively slow market uptake. Let's find out why…

By Luke Perkocha



Eight years ago, I spoke about the business case for "digital pathology." Here, I will revisit the topic with the hindsight of the last eight years. Where does the business case exist today? What are the key factors to consider before adoption? And how should decision-makers react to the ever-increasing "push" to go digital?

Let's begin by clarifying the term "digital pathology," because it can have broad or narrow meanings. I define it broadly as "the use, including display and analysis, of digitally acquired images of pathologic specimens (gross, histology or cytology) to accomplish a clinical or research objective." By this definition, digital pathology can range from photomicrographs taken with a microscope-mounted digital camera, to remote viewing of video images, to digital whole-slide imaging (WSI) – this encompasses viewing and interpretation of the digital images by a human being, as well as manipulation, analysis or interpretation of digital image data by software.

Being mindful of this broad definition is important, because many think only of WSI technology as "digital pathology," which misses compelling business cases for other uses of digital images. However, WSI is the digital technology that requires the largest institutional commitment and investment, so it is WSI that is the focus of this discussion.

The radiology–pathology comparison story

To understand the current state of WSI, it is useful to consider digital radiology's adoption story. When WSI was first introduced, one often heard, "Look how digital imaging transformed radiology. Soon, pathology will also be all-digital – it's inevitable!" But drilling down on the transformation of radiology from film-based to digital, it becomes apparent that the comparison of WSI to digital radiology, as a transformational technology to move pathology from slide-based to digital, doesn't go far. The hurdles to WSI adoption by pathologists are similar, but the benefits are not comparable.

Digital radiology did four major things that advanced the business case for that technology:

1. **It ultimately removed costs from the system.** True, the new digital imaging technology required substantial startup and maintenance costs, including digital-capable X-ray and CT scanners, high-end workstations and display screens, abundant digital storage, high-bandwidth networks, and sophisticated software for processing, analysis and image storage and retrieval (PACS), as well as trained IT staff to install and maintain these systems. But the transition also eliminated many costs forever – including all of those associated with developing and printing film-based studies, toxic chemical disposal, maintenance of film libraries, and all associated staff costs that went with film-based radiology.

2. **It improved the workflow of radiologists.** Digital technologies markedly increased radiologists' efficiency and mitigated the impact of a then-looming shortage of radiologists. Pre-digital, radiologists sat in front of giant film alternators, large devices loaded with hundreds of films for scores of patients, which mechanically sorted and moved them into position for viewing. This was slow, inefficient and labor-intensive, but still much faster than digging through piles of envelopes on a table or film library shelves. Once digitized, current and prior studies could be called up on a workstation in seconds for comparison. Digitization also allowed for business models that located credentialed radiologists in different countries and time zones to provide immediate interpretations of studies done anywhere in the world on a 24-hour basis.

3. **It allowed for new analyses of radiologic images.** This improved diagnostic accuracy and created new diagnostic applications. CT scans were the state-of-the art imaging technology pre-digital. But these required radiologists to hang multiple films in sequential order on large screens and slowly move through planes of the patient's body to identify disease. Digital films could be viewed in "stack mode," allowing the radiologist to page through a large set of images quite rapidly (critical as the number of images per study increased dramatically). A 3D representation could also be created from a sequence of images and rotated and viewed from different angles. Many other types of "digital-assist" technologies have been developed and used to interpret both 2D imaging and a

host of new 3-D acquisition technologies. None of this would have been possible in film-based radiology.

4. **It had a tangible impact on "quality."**
   A little-remembered aspect of pre-digital radiology was the loss of large numbers of patients' films forever – either misfiled in the library or checked out and never returned. Like in pathology, some radiologic findings can only be interpreted when a current study is compared with a prior one and a key change is spotted. It was not unusual, in busy medical centers, for 10 or 20 percent – or even more – of the films in a library to be lost, and the impacts on patient care are obvious.

What about WSI in the pathology setting?

Does it ultimately remove costs from the system?

Although it suffers from the same hardware, software and IT costs as digital radiology, WSI doesn't eliminate any of the costs of slide-based pathology, as going digital eliminated all the costs of film-based radiology, because WSI still requires the glass slide as a starting point. In fact, WSI increases some costs – for instance, WSI imagers' focusing algorithms require a much better-quality glass slide than human pathologists, who can focus up and down or ignore preparation artifacts. The WSI imager's rejection rate requires more recuts and sets the bar higher for slide quality. Use of whole-slide images also requires more processing power, storage capacity and bandwidth than digital radiology images – why? Because they're in color, and because even "2D" images are actually 3D because of the focusing planes in a slice of tissue on a glass slide. These factors increase the cost hurdle for digital pathology. What about glass slide storage costs, often cited as a business justification for WSI? Unlike in radiology, the relative cost and space requirements of a decades-long archive of glass pathology slides are actually quite manageable.

Will it improve the workflow or efficiency of a pathologist?

This is also a frequently-heard business justification for investment in WSI. To even consider answering "yes" requires a "perfect world" of complete adoption – a leap from the current state in most clinical settings. What would that perfect world look like?

- All slides on all cases would be imaged.
- The imaging archive would be maintained on a pathology PACS system integrated into the anatomic pathology laboratory information system (AP-LIS).
- Pathologists would need workstations with adequate processing power, high-quality display capability and sophisticated human-interface technology. The workstations must function like a microscope currently does – letting users rapidly view all parts of a slide at multiple magnifications and in multiple focusing planes.

But this perfect WSI system doesn't exist, although it has long been the "Holy Grail" of otherwise very capable technology companies. Various halfway measures that have been advocated for WSI, like only imaging key slides (or only cancer cases, or only consultation cases, or only tumor board cases…), are ways to mitigate the cost – but because they still require glass slides, they're inherently costly and inefficient, especially if the digital images aren't completely integrated into the AP-LIS and require a separate program to view and manipulate.

Where can WSI improve pathology workflow and efficiency today? There are narrow applications where it's already a reality – most notably, the remote interpretation of urgent cases or frozen sections that would otherwise require either the pathologist or the slides to travel. That's especially useful for rural and specialty hospitals, or for cases that require subspecialty attention. Such productive uses of WSI improve the workflows of individual pathologists by sparing them long-distance or out-of-hours travel and ensuring that they can get (or give) answers in a timely manner. Although these applications of WSI contribute to the

"Although these applications contribute to the efficiency of the individual pathologist, as well as the pathology workforce in general, the gains they offer aren't comparable to those radiologists saw in their transition to digital."

efficiency of the individual pathologist, because the proportion of such cases needing remote interpretation is small, the gains in efficiency aren't comparable to those radiologists saw in their transition to digital.

Will WSI allow for new types of machine analysis of pathology slides?

In this area, WSI does indeed have promise. Various forms of image analysis are already available that take advantage of digitization. The most widely adopted example is the use of imagers to screen liquid-based cervical cytology preps – truly a success story in the application of digital pathology imaging. Similar applications in histology might include identification of "rare events" in biopsies, such as cancer cells among benign cells, or an acid-fast bacterium on a stained slide. Another real-world analytic application is in the scoring or quantification of characteristics on stained slides – for instance, the percentage and intensity of cells staining for ER/PR, or the proliferation index using Ki-67-stained slides. Some researchers are even working on algorithms to allow software to learn from "viewing" digitally imaged pathology slides – with the goal that someday, computers might become artificial intelligence-enabled diagnosticians capable of assisting or even replacing pathologists ("computer-aided diagnosis").

Although image analysis is an exciting business justification for WSI, the range of applications for which it's currently needed is small, and competing technologies like liquid biopsy, molecular techniques or in vivo microscopy are ultimately likely to advance faster, and be adopted more widely and cost-effectively, than WSI.

Can WSI have a tangible impact on "quality" in pathology?

Here is an area where WSI has real-world applications today, and one of the best business justifications for the technology. In areas like education, competency or quality assessment, and consultation on select slides or cases, WSI can be much more cost-effective than formats requiring transportation of a physical slide. WSI is already used to teach the younger, more "digital-friendly" generations in medical schools, and it's expanding into residency training programs and continuing education for experienced pathologists. In competency assessment, too, digital images can be used to assess practitioner competency and quality in a standardized way – something Canadian pathologists have already pioneered on a provincial basis.

WSI can also be used for consultation on difficult cases. Many diagnostic concordance studies have shown that pathology is very much an interpretive and subjective specialty, one which is best practiced in a consultative environment – and WSI can facilitate rapid and simultaneous consultations from multiple colleagues. This application of WSI has not seen enough investment. There could be a few reasons – resistance from pathologists uncomfortable with viewing slides digitally; a lack of well-developed payment models; institutional IT limitations; or fear of legal consequences like malpractice, running afoul of patient privacy laws, jurisdictional licensing or other regulatory requirements. Despite its utility, the business case for this application has not been well-made. The costs and benefits have been poorly measured, defined or presented, and many times, the cost has been inflated by presenting unnecessarily expensive "all-digital-lite" plans.

Let's take a broader view

While this comparative look at the adoption of digital radiology and pathology through the lens of the business case can be useful, there are a few key aspects not illustrated by the radiology–pathology construct.

The first is the broader definition of "digital pathology," which includes modalities other than WSI. This is important because these technologies are much less expensive, more widely available, and often very much adequate to the task at hand. They include microscope-mounted digital cameras (or even smartphones!) whose images can be used for education, quality assurance, consultation, remote diagnosis or triage, or in communications between pathologists and clinicians to facilitate patient care. A "store and forward" model using a simple photomicrograph of a key slide can transform a time-consuming process (sequentially transporting a glass slide from one person to the next) into a time- and cost-efficient consultation with multiple colleagues simultaneously that can be key to quickly and accurately diagnosing or triaging a tough case. Streaming video can also have real-world uses – for instance, in the operating room, for frozen sections, or during regional tumor board meetings. In part due to the focus on WSI, the benefits of these lower-cost applications have not been fully realized, nor the workflows optimized. While WSI can also serve these needs, it's much more expensive and the additional benefits may not be worthwhile.

A second aspect to consider is the possibility that fundamental changes in market structure, the legal and regulatory environment, the cost of WSI, or a breakthrough in technology may alter the cost-benefit calculation. What if a marked shortage of pathologists occurred in a region, or a large new market opened? What if regulatory or licensing barriers fell, so that foreign-licensed pathologists or even non-pathologists could read cases at significantly lower cost? What if the cost of WSI plummeted due to a technological advance – say, something that eliminated the need to produce a glass slide? Or there was a compelling breakthrough in artificial intelligence, machine learning or computer-aided diagnosis? Such events may seem unlikely, but could well change the calculus for the business case for a technology

like WSI. The impact of a different environmental context on the case for WSI is illustrated by its accelerated adoption in some companies in limited research or in veterinary medicine settings (where the legal and regulatory barriers are lower, business uses differ and the pathologists may be fewer and farther between), as well as in unique clinical settings like rural and specialty hospitals (where external factors justify the necessary investment).

The reality check

Although WSI is now a "maturing" technology, there is not yet a compelling business case for wholesale deployment. However, WSI and other digital technologies are certainly of value, and I believe they will – and should – be adopted when the use case is appropriate. It is also prudent for pathologists to keep an eye out for potential "killer apps" or environmental changes that could upend traditional practice. But at the same time, it is important not to underestimate the efficiency of a pathologist looking at a slide on a microscope, or the cost and difficulty of radically changing that time-tested workflow using a single technology like WSI. Any such change requires a critical analysis of costs and benefits much like the one conducted in radiology – despite the not-insignificant proportion of radiologists uninterested in "going digital," the move made sense. That's not currently true for WSI, something the market has validated by its slow uptake of clinical WSI over the past decade. It is important not to be overly wowed by a technology for its own sake. No matter how "cool" it is, one always must ask, "Is this a 'solution in search of a problem,' or a real game-changer?"

In a nutshell...

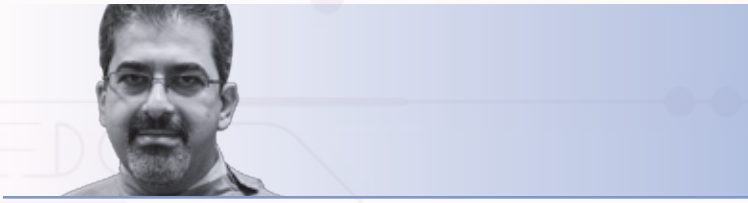
- **Pathology and radiology aren't equal, and the arguments for radiology's digital transition don't necessarily hold true for pathology's**
- **Digital pathology holds promise for image analysis and quality assessment, but other applications don't make financial sense – yet**

Luke Perkocha practices anatomic and clinical pathology, with a subspecialty in dermatopathology, at Kaiser-Permanente in Northern California. He has a degree in business administration and writes and speaks about business and technology/informatics topics in pathology and laboratory medicine.

A Roadmap to the Future

A careful flow analysis and roadmap can be the key to a strong business case

By Alexi Baidoshvili



We are one of the first laboratories to move to a fully digital histology workflow – and possibly one of the first to have made a case for doing so. It seems to me that very few people in the pathology world believe that such a business case can become possible. LabPON has made the transition, though, and among the many things I gained from that is a certainty that the long-term benefits outweigh the costs.

Getting off the ground

Our first business case was based on assumptions – which is what you have to do when you're trying to pioneer something new and nobody is sure what to expect. We made some calculations and took some educated guesses, but there was no way to be certain until we actually implemented our plans. Now that we've gone fully digital, we know what needs to be done to get there. That's why, in 2015, we started a new flow analysis – one that, when we finish at the end of this year, should be accurate, informative, and lead to a much stronger business case for digitization.

There are two components in a business case for digitization. The first is logistics. It's no challenge to demonstrate that there are clear logistical advantages to digital pathology. You don't have to go through your physical archives anymore; you don't need a secretary to manage your storage and filing systems; and you can save money by optimizing your staff and space requirements.

The second component is diagnostic time – and there are also benefits to be had here. I am sure that when we finish our flow analysis, we'll be able to show that digital diagnostics, including viewing slides digitally, is faster than the microscope. I think that, based on our preliminary results, a combination of the logistical and time-based benefits might allow pathologists to do their diagnostic work faster. That means you increase both capacity and efficiency. Not only that, but I think that – at least in part – the quality of digital diagnostics is actually better than

that of slide-based work. If our final analysis confirms these preliminary results, then that's big money – and big benefits for pathologists.

Finding funding

Fortunately for me, LabPON is a non-profit organization. We're not part of a hospital, nor are we private – which means that we don't have to build a very detailed business case in order to obtain financing for a new project. So at the beginning, we calculated the investments we thought we would need – things like new scanners and digital storage – and explained the profits, not just in terms of financial benefits, but also quality improvements and increased flexibility.

Our laboratory works for four different hospitals in the area, and our pathologists travel a lot. They attend multidisciplinary meetings, examine frozen sections, and do all sorts of things that traditionally require their physical presence. But as a result, they're sometimes stuck at the hospital for several hours in between tasks – a waste of time for them and a waste of resources for us. But now, with digital pathology, they can do their diagnostics remotely from the hospital, or even from home. It creates a lot more flexibility, as well as improving the quality of the diagnostics, both of which factored into our initial "business case." That message was what originally drove us to consider digital pathology, and strong enough to convince the board of its value!

A leap in logistics

In my laboratory, a glass slide has a long journey to complete. Once it's finished and the coverslip is placed, a technician checks the lab management system, assigns the case to a specific pathologist, and takes the slides on a walk through our three-floor building to its destination. When the pathologist is finished with the cases, the slides are taken back to the archive. This happens five or six times a day, and we have two or more multidisciplinary meetings a day that also require the retrieval of slides from the archive. It takes a lot of people – and a lot of time – to accomplish all of that moving around. With digital slides, this transportation of physical slides is not necessary. The pathologist can simply enter a number into the image management system and see the corresponding slide. That saves so much time and effort that we actually need fewer personnel – in our case, we can reallocate a secretary and a technician to other work, just by eliminating those unnecessary logistics.

The work doesn't just get faster with digital technologies; it gets more convenient, too. When I'm preparing for a multidisciplinary meeting and need to refer to a particular slide, I have to go through a folder full of slides, check them, read the patient's reports, locate the ones I need, and write up the cases and slides to be discussed – all while using the microscope as a reference. But digitally, I open the case in the lab management system, which is fully integrated with our image management system, and I can see the whole-slide images and reports on my screen right away. And when I'm in a meeting and someone brings along an extra case for advice, I no longer have to say, "Sorry – this is new to me and I don't have any information with me." Instead, I can just log in remotely from the meeting room, look at the slides for that particular case, and then provide an opinion. I use the technology when I'm working on cases in the laboratory, too. For example, if I encounter a lymph node with potential metastasis and I'm not sure whether or not the tissue has the morphology of the patient's primary tumor, I no longer have to ask my secretary to retrieve the primary tumor slides from the archive. Instead, I open the case in the lab management system, juxtapose the old and new images on the screen, and compare. What used to take me minutes now takes me seconds!

> **"Most people think that the biggest investment will be the scanner or the software. That's not true. One of the biggest investments is the transition period."**

Words to the wise

Before pathology labs begin the digitization process, it's vital to establish a good flow analysis. Why? Because most pathologists think that the only part of the flow that needs to change is the part after the slides are ready to be scanned. But that's not true. To make the jump from microscope to digital, there's a high likelihood that you will need to change multiple aspects of your workflow. That can be difficult to understand if you haven't actually transitioned yet – but we certainly changed a lot of things in the early part of our flow. From the information in the lab management system (which has to be linked to the image management system) to the protocols we use in the cutting room (which now minimize the number of slides needed per case to save on storage and scanning time) and the stains we use for immunohistochemistry, many things are different.

So you need to make sure you've done a good flow analysis before you begin. You also need to make sure your laboratory has a good network – because if it's slow, you'll lose time – and that involves checking everything from cables to switches.

The laboratory will need an image management system that can be fully connected to the digital pathology system. You also need to make plans: how much digital storage will you need? How long will you keep digital files? How many scanners will you need to handle your highest workload? And ultimately, the answers to all of those questions will lead you to your roadmap and business plan.

One thing to remember, though: most people think that the biggest investment will be the scanner or the software. That's not true. One of the biggest investments is the transition period. That's when you have to sustain duplicate logistics – slides and digital files – but you can't overlook its importance. Pathologists need to learn to trust digital images, and they need to have glass slides to check if they want to verify that the image was captured well and they've made the right diagnosis. During the transition period, pathologists will naturally work slower as they check both types of image, and you'll need more personnel because you have additional logistics. What if you don't have the personnel – or the money? You can't skip the transition period altogether, but you can make it shorter. How? With a good flow analysis and a good roadmap.

That's my secret in a nutshell. If you want to make a good business case for digital pathology, you have to plan ahead. Figure out what you want your digital laboratory to look like, what changes you need to make, and where you need to spend your money (on both direct and indirect costs) – and when you have the answers to those questions, you should be able to make a smooth transition and get a good return on your investment.

In a nutshell...

- In the long-term, digital pathology's benefits outweigh its costs; it simplifies logistics, saves time, and allows pathologists to work more efficiently
- Before going digital, it's vital to establish a good flow analysis and roadmap to make the transition short and seamless

Alexi Baidoshvili is a pathologist and project director of the digital pathology team at LabPON, The Netherlands.

Part of a Larger Whole

Digital pathology can provide great return on investment – but only if laboratories are ready for a sea change

By Marcial García Rojo

Digital pathology is expanding in daily practice. More and more groups are moving to a totally digital histopathology service, spurred on by the practical experience of the pioneers. It's limited experience, of course – only a few years' worth – but it has demonstrated that digital pathology can be a reality. And the fact that some brave people are working fully digitally now is key, because they're encouraging others to take the same step. There's a distinct change in attitude – nowadays, pathologists can see the speed and accuracy of digital diagnosis, and they recognize that the technology isn't as distant or as scary as they thought. This is especially true in institutions where telepathology is necessary – for instance, if they need the services of a particular specialist, but don't have one on staff. Overall, I'd say that, in the last three years, digital pathology has changed from a sporadic phenomenon to a widely known and increasingly popular option.

Watching your workflow

When I ask why laboratories choose not to adopt digital technologies, I often hear, "Well, we have other priorities." They feel that they have other problems to solve – things like buying needed equipment or moving into new techniques. But in hospitals where the basic problems are already solved, digital pathology is a real priority. They've realized that it can help them optimize the way they work.

Unfortunately, the financial aspect rules much of the decision-making. Digital pathology offers a return on investment – but only if you're ready to do it from a global perspective. You have to be willing to change your workflow and move people from tasks that are no longer needed (like delivering glass slides, or searching through archives) to ones that still are. Of course, it doesn't all happen at once – you start with duplicate processes, glass and digital, and you have to make allowances for both. It can be difficult to convince those who control the purse strings to invest in digital storage without eliminating the physical. Nowadays, though, the

options for inexpensive long-term storage are multiplying, so the main investment is in short-term storage – which requires much less capacity. With a sensible plan for storage, any laboratory can make a good return on digital pathology investment.

Why isn't everyone seeing such a return? I often see laboratories focusing on a single solution rather than their global workflow. For instance, they'll decide that they want a scanner for digital image analysis – but if it isn't part of a bigger picture, it will be a very expensive solution to a single problem. You have to be willing to make a wholesale change; for instance, it's a good time to apply Lean technology or Six Sigma. It's a good moment to improve every single step of your laboratory's process. It sounds like a lot of work – and it is a lot of work – but after you work hard for a few months, you get the payoff for years.

Serendipitous solutions

In my laboratory, we call our transition "serendipity" because everything aligned just right to make it happen. The most important thing, though, was our engineers' willingness to take on a new project. We told them, "There's one really complicated thing we'd like to do: manage all of the large images we capture using digital pathology techniques." They agreed that it was a difficult task – and that's why they wanted to work on it. We were lucky that they wanted to collaborate with us on it! It's not enough to have a supportive organization or an innovative team that wants to transition to digital; you need good support from your computing department. Without them, we'd have been lost.

Ultimately, I hope we'll end up with universal technology solutions. Things are a bit fragmented right now; each digital pathology company has its own formats and standards. When those companies realize that they need to use a common format, so that we can all view and manipulate slides regardless of how they were produced, things will become much easier. I understand that each company wants a proprietary solution, but I think it's vital for them to understand that we – the pathologists – really need a single standard, like DICOM. Having to change from one format to another adds an extra step to the process, complicating it and potentially impacting patient care, and the only way around that is to share a universal format.

Once we've accomplished that, the next step is to address storage. Pathologists are being treated like we need a specific solution – but we don't. We simply need the same kinds of solutions as radiologists, endoscopists and others already have. The problem is that there's always more information to be managed. When the price of storage decreases, we allow ourselves to image in 10 planes instead of just one. Then we create 3D images instead of 2D. Then we increase the resolution. And with each change, the image size increases – and with it, the demand for storage. In the end, it's up to us to be aware of what is useful for diagnosis. Do we really need 3D for everything? Do we really need to capture all our images at 60X resolution? Technology will continue to improve, but we have to find a balance between what we can do and what is worth doing.

> **"We really need a single standard, like DICOM."**

A marriage of man and machine

With AIDPATH – the Academia and Industry Collaboration for Digital Pathology – we've been working hard to compare different image analysis solutions with each other and with manual methods. Although there are differences between manufacturers, we've realized that some of the discrepancies are due to human error. The pathologist selects what needs to be evaluated in each image, which means that no matter how well the technology itself works, there's still a human factor involved that we can't control very well. For instance, what if the user selects an area of in situ carcinoma instead of infiltrating carcinoma? or misses a region of a tumor image with high expression of a protein of interest? The conclusion I've reached is that we need solutions to help pathologists locate the most interesting parts of biopsies. For instance, it would be very interesting to design algorithms that can help inexperienced pathologists locate infiltrating carcinoma, or detect areas with the highest biomarker expression. Some of these types of algorithms are already in development, and they're working very nicely so far. Perhaps this is the beginning of a beautiful partnership between humans and computers!

In a nutshell...

- Many laboratories have other priorities to address before going digital, but for those that are ready, it can help optimize their work
- To gain a return on investment, the digital transition has to be global – not just a partial change to the workflow, but improvements to every step

Marcial García Rojo is the principal investigator in the EURO-telepath EU project, a principal researcher with AIDPATH, and head of pathology at the University General Hospital of Jerez de la Frontera, Spain.

Techniques in Transition

Flexibility and computer-aided diagnosis can help digital pathology gain a foothold… but is the technology ready yet?

Michael Schubert interviews David Snead

When it comes to "going digital," pathologists fall into one of three groups: early adopters who are very enthusiastic, people in the middle who are unsure of its benefits, and those who are adamantly opposed to it (whose opinions range from skepticism to outright hostility). At the moment, I think it's the early adopters who are driving the digital movement. That's not to say that the skeptics are wrong – but pathologists are scientifically trained; they want to see evidence, and although there's plenty of evidence to say that digital pathology is no worse than a light microscope, there's no real proof that it's better. It's not an unreasonable view. What is needed is more evidence of a return on the investment required to go digital.

Return on investment

The first of these and most significant returns comes from the flexibility of workload distribution. That means convincing pathologists that they can report cases to hospitals other than their own. Once they buy into that, the traditional model for cellular pathology (where hospitals maintain their own laboratories with their own pathologists) breaks down completely. Instead, each hospital makes its own provision for pathology – and that might involve the use of remote reporting of sections via digital pathology. Why? Because some tasks are specialized, and it makes sense to have them performed by experts. Renal biopsies are a good example; it's a complicated, small-volume area, requires some out of hours reporting and is very difficult for those who lack expertise – but if you are a renal pathologist it is feasible, and probably desirable to grow this workload by reporting renal biopsies for hospitals other than your own. By outsourcing this work, a hospital pathology department can concentrate on the volume specialties that it routinely deals with. Hospitals dealing with heavy workloads and often shorthanded through temporary or long term vacancies can use digital pathology to allow off-site reporting, either by locum pathologists or established consultants keen to work additional sessions. This avoids the need for travel, increases the pool of available expertise and can avoid expensive agency rates.

The other major promise of a return on investment is computer-aided diagnosis. There is very little of this actually in practice today but the potential is enormous. The spiraling demand for histopathology with our current aging population means histopathology needs increased automation and tools that improve pathologist's decision-making ability. Automated slide review, mitotic counting, or tools that analyze biomarkers and grade tumors. These are all things that pathologists do every day, often not as well as we would like to think. We're quite good at working out what's abnormal – but our human eyes and brains struggle with objectively quantifying exactly how abnormal it is. So this is the next big thing in digital pathology… but it's not ready yet. We don't have the mitotic counting and tumor-grading algorithms we really need.

> "The only sensible reason to change to digital at the moment is to provide flexibility for slide reporting. At least in the United Kingdom, we just don't have enough pathologists right now. Digital pathology offers a theoretical solution to the problem."

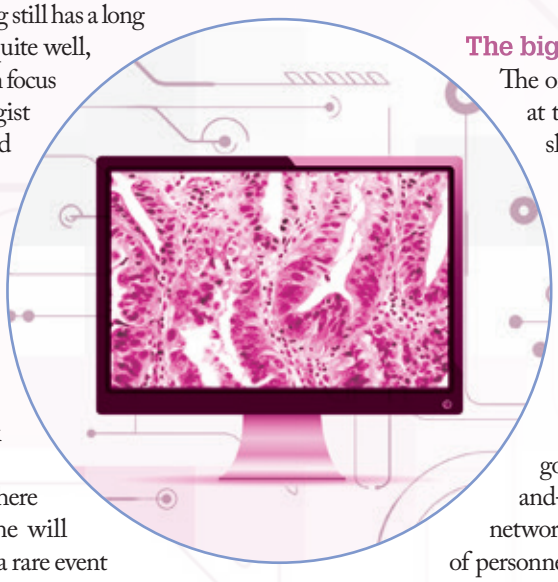
Algorithm development

There is some research around algorithm writing and development. There is not enough and it is limited in its extent. However, although showing some promise, these studies have not not been translated into practice for full-scale trials. There's a much bigger step than most people realize in translating a written algorithm into a piece of software for diagnostic workstations, and most research teams don't have the resource to do this, and many institutions active in this arena lack partnership with pathology labs with the IT infrastructure to support this sort of translation.

Our team at the newly established UHCW Centre of excellence for digital pathology are working on tumor grading. We've broken it down into the same parameters that are used for breast cancer grading – mitotic rate, nuclear pleomorphism, and degree of tubular differentiation in adenocarcinoma – and modeled each element with an algorithm. We've had some success, but the difficulty lies in getting good enough results from each parameter.

The results thus far are definitely showing efficacy, but at some point we need to draw line, stop improving the algorithm, translate it, and evaluate how it actually works in a full-scale clinical trial. That will be an expensive step, but a valuable one – and one we hope to take in the next year and a half.

One thing we've learned is that scanning still has a long way to go. Modern-day scanners work quite well, but they have quite variable focus. They can focus most of a slide well enough for a pathologist to make sense of it, but that isn't good enough for algorithms. Algorithms will not work on areas that aren't perfectly in focus. So part of our current work is on a program designed to measure the slides' degree of focus. That way, we can feed in only the appropriate cases and increase our success rate dramatically. Improving scan focus quality control is a key element to getting algorithms to work successfully in real-time.



You've also got to take into account where the algorithm is designed to act. Some will operate upstream of the pathologist, like a rare event detection tool we're developing to find melanoma in sentinel node biopsies. The slides will be exported from the scanner to a server, where the algorithm runs, finds the area of interest, and the annotated slides are then returned to the pathologist reporting pool for review. That algorithm, which is designed to work on a server in the cloud and process massive numbers of slides from multiple centers, places special demands on the technology, which requires solving prior to roll out. You need software to sort slides at the source, send them to the cloud, bring them back with annotations visible on multiple viewing platforms with complete resilience and accuracy, and it has to be secure. None of this is new to the industry but much of it is to histopathology so we need to learn and catch up.

Other algorithms work downstream of the pathologist. That is, the pathologist identifies the slide's area of interest and then passes it on to the algorithm – like in ER staining in breast cancer, where the tumor is manually identified at diagnosis and where estrogen receptor, progesterone receptor and HER2 are stained on sequential sections but scored according to the originally identified region of interest. These algorithms combine overlay steps identifying the region to be scored and then the scoring itself. Still others will work under the supervision of the pathologist, such as tumor grading tools performed at the point of the diagnosis. These will need to run on the workstation in real-time to allow the minimum of disruption to workflow.

Therefore, what the algorithm is doing places some demands on the way it needs to be designed from the ground up. You can't do this later in the process; it has to be envisioned right at the start so that you can predict your software requirements. It's not something most people think about, though. It's only when you start to work with algorithms that you realize how much these things matter. And only when you find ways of addressing those issues can digital technologies truly support the work of pathologists.

The big picture

The only sensible reason to change to digital at the moment is to provide flexibility for slide reporting. At least in the United Kingdom, we just don't have enough pathologists right now. Digital pathology offers a theoretical solution to that problem – we can reorganize ourselves as digital hubs and redistribute our slides so that we get better efficiency from the reporting manpower that we already have.

To administrators, I would say, "You've got to think big." think about creating hub-and-spoke laboratory models and setting up networks to address the deficits caused by a lack of personnel. Digital pathology can solve many of the problems with those kinds of transitions – and that's a major driver, because at least half of pathology labs in the UK right now are severely understaffed. If you give existing pathologists the work they do best, allowing them to properly subspecialize, rather than work on what has got to be done because there is no one else to do it, they work faster and more efficiently. I also suspect that it would reduce error. Error is very expensive in pathology, so the better you are at getting the answer right – which means giving pathologists the work at which they excel – the more costs, and lives, you can save.

In a nutshell...

- **The greatest benefit of digital pathology lies in increased flexibility, which can help balance out the widespread shortage of pathologists**
- **Computer-aided diagnosis may also provide benefits one day – but the algorithms aren't quite ready yet**

Professor David Snead is Clinical Lead for cellular pathology at the University Hospitals Coventry and Warwickshire NHS Trust and Coventry and Warwickshire Pathology Services. He is the Director of the UHCW Centre of Excellence for Digital Pathology and Professor of Practice at Warwick Medical School, UK.

A Business Case for Common Sense

Good return on investment is more than just a strong business case on paper – you need to consider the practical workings of your laboratory, too

By Liron Pantanowitz

For me, the return on investment of digital pathology is about more than just the business use case. It's about how the system is used – how it truly meets the use case. Much of the time, people justify the need for a new system on paper but then don't use it to the full extent of its capabilities. The idea is attractive, but the technology itself doesn't fit into the overall workflow. People say, "Buy digital, start slow, and scale up," but when it's disruptive and poorly integrated, that's hard to do – and then the scanner ends up gathering dust in a corner! That's what I think differentiates good digital pathology setups from bad: how well they're used. A bad system is purchased for novelty's sake, or to meet a niche need; a good one facilitates faster, better, scalable work throughout the laboratory.

Versatile vendors

Labs need to view their vendor-client relationship as a true partnership when embarking on their digital pathology journey. Digital pathology is always evolving, so you're going to need to work closely with your vendor to help you adopt and customize your system – and if you don't have that kind of relationship, you've made a bad choice. That's especially true because, with new technologies, you get what you pay for. You obviously have to set your budget wisely – but if you buy something inferior, it might not perform the way you want. My personal key features are "plug and play" simplicity and interoperability; I don't want to be locked into a specific file format or application, because no one product can do everything, and you need freedom and versatility to grow.

It always comes back to integration. There's a lot of vaporware out there that vendors have promised will integrate with other systems, or will have high uptime and low scan failure rates. But you only truly know what those numbers will look like when you flip the switch on your own system. Of course, you can't buy a system "on spec" just to see how well it will perform – so instead, you have to speak to existing users and find out what they think. That can be difficult if you're an early adopter like we are at the University of Pittsburgh Medical Center. There aren't too many labs that have extensive experience with new systems before we do!

> "When we worked out the net difference, our system saved approximately US$18 million! Based on that calculation, our administration gave us the green light to roll out digital pathology – and in five years' time, we'll know whether or not we were right!"

What is "fully digital?"

I have a problem with the "fully digital" concept. Ideally, if you're making a commitment to digitization, then fully digital is the way to go – but I think that's a misnomer. Most labs aren't really fully digital; they're mostly digital, because they exclude certain use cases like cytology or hematology. That means they still have microscopes, and the minute you keep microscopes around, you have a hybrid workflow, and it's naïve to think you can avoid the need for extra personnel or extra work. But it's also naïve to think you can go fully digital, because not every case is appropriate for scanning – and because there'll be times when you need to troubleshoot, or when the digital system is down and you still need to deliver care.

Lessons Learned

By Liron Pantanowitz

Digital pathology is not just about the tech. You have to consider the practical impact that technology has on the people who use and maintain it, and on how it affects their day-to-day work. Here's what we learned during our own transition to digital:

- Pathologist training and engagement is absolutely key.
- No matter what you're told about scanning or turnaround times, you'll only figure out what your personal times are when your own laboratory goes live.
- Pre-imaging factors (like making sure you have hands-free operation, good slides, and careful calibration) are equally or more important than the imaging itself.
- Incremental deployment is better than immediate adoption, because it allows you to continually adopt new technologies as they emerge and evolve.
- Don't get locked into a single vendor, system or image format; otherwise, you won't be able to integrate with different platforms.

But I think that actually helps with the transition. Initially, pathologists need to learn to trust the new system, so they run it side-by-side with the old. They don't give up the microscope completely because it's a reassurance. And I think that's exactly how we should be practising. We shouldn't be cowboys! We shouldn't be too gung-ho about diving headfirst into digital; it's going to take time, and it's wise to have a backup. I just think we need to be aware that when we say "fully digital," what we're actually aiming for is "almost fully digital."

A fundamental shift

Over the last 10 or 15 years, I've noticed a shift from hardware to software to content. In the beginning, there was an emphasis on improving scanners and extending their capabilities; later, people began focusing on image management and sharing software. But in the last five years or so, there's been an upsurge of interest in algorithms, apps and analytics. That's shifted the return on investment. In the beginning, when we were talking about hardware, everyone wanted to scan their slides. Then, when we started to think about software, it was worth going digital because the ability to store and share images meant we could introduce efficiency and explore telepathology. Now we're looking into what we can do with apps and algorithms that a microscope could never do – things like image analysis or content-based image retrieval.

My analogy would be the cellular phone. In the beginning, people worried about which device was the best. Then, they worried about which operating system was the best. Now they don't really care about either – what they care about is the apps they use, and I think digital pathology has followed a similar path.

Weighing worth

I think telepathology is still the area where digital pathology delivers the best return on investment. It allows you, as a pathologist, to do three things:

1. Balance your workload, so that you can be more efficient. Labs want to get their results out quickly and cheaply.
2. Provide coverage and care where you couldn't before, so that you can extend your reach. Covering frozen sections at remote hospitals allows surgeons to operate there, whereas previously the patient might have had to travel.
3. Centralize your services, so that you don't duplicate costly services in multiple locations. For that matter, you don't need to duplicate pathologists, either; instead of having expert generalists at every hospital, you can subspecialize, sending each pathologist the cases in which they excel and reaping the best return on investment.

Equally, some things are not worth the expense right now. For instance, I no longer think it's worth scanning every slide you encounter. It doesn't make financial sense if you have ready access to the physical slides; it's only necessary when you don't. I also don't think labs should be investing in algorithms and apps that aren't FDA-approved. Vendors offer us these things, but they don't take them through regulatory approval first, which means we can't base patients' treatments on the data they provide, so I don't think they offer a good business case for a digital transition. Before we can use those apps in a clinical environment, someone has to spend the dollars needed to gain FDA approval.

The other thing that ends up being both frustrating and expensive is that digital pathology systems tend to be standalone – so they don't work well with existing technology. It places great demands on IT staff to learn, integrate and maintain this "special" system, which results in high indirect costs. It's like owning a Ferrari – you buy it because it's beautiful and runs well, but when it's time for a service, you realize how expensive it is to maintain. Indirect costs make up the majority of digital pathology expenses; you have to consider who's going to maintain the equipment, who's going to scan the slides, where you're going to store your images, how you're

going to change your facility and network setup, and even what peripherals you'll need in addition to the scanner.

But those investments don't go to waste, because there are significant sources of potential savings and income as well:

1. Insourcing new business – whether it's offering second opinions via telepathology, acting as a reference lab, or digitizing immunostains for clients; all of that can bring in new business use cases for your lab.
2. Hiring fewer pathologists in areas experiencing staff shortages. Multi-hospital systems can replace some pathologists with scanners, so that instead of keeping consultants in labs with low-volume workloads, you can install a scanner and send images to consultants at central locations.
3. Reducing inefficiencies in the lab. Our time and motion studies found that pathologists can waste more than 13 percent of their time on administrative duties (1), with travel and archived slide retrieval on top of that. Digital pathology eliminates a lot of those inefficiencies and increases the time pathologists can spend working.

To come up with a hypothetical dollar amount, we did a novel study looking at the top 12 misdiagnosed cancers in our healthcare system (2). Then we looked at the potential cost of making a misdiagnosis – not just in terms of litigation, although we included that, but in terms of over-, under- and delayed treatment as well. We compared that to the cost of buying a digital pathology system and rolling it out over five years, so that every hospital was connected digitally and cases could be distributed to subspecialists for faster, more accurate diagnosis. When we worked out the net difference, our system saved approximately US$18 million! Based on that calculation, our administration gave us the green light to roll out digital pathology – and in five years' time, we'll know whether or not we were right!

Four for the future

I see four things in digital pathology's near future.

First, FDA approval is going to have a major impact. It's going to encourage widespread adoption of digital pathology, but only then will people realize that this is just the beginning. Once we have approved devices, we'll need approved software, approved apps, and so on – an endless crusade.

Then, I think we're going to see more and more new vendors entering the market. I'm talking about companies like Facebook and Google, because they already have the technological chops – they just need to apply them to healthcare. Once they see that we've overcome the major hurdles, they'll likely start applying their tools. Hopefully, that will drive down the price of digital platforms, because the emphasis won't be on the hardware; it will be on the applications, which brings me to the second thing that will feature in the next generation of pathology. When this happens, we'll finally have the opportunity to see some real "killer apps." Killer apps sell platforms – take the Atari system, for instance; it wasn't very good, but when Space Invaders came out, everyone ran out to buy an Atari. Digital pathology needs the same thing, and I think we'll see it happen when some other, bigger players join the field.

Next, I think the industry will be forced to standardize. As we adopt digital platforms and integrate with more and bigger systems, we'll have to fit into enterprise imaging initiatives. I can't say which standard format will be adopted, but there will definitely need to be some standardization – and I think it's long overdue.

Finally, I'm concerned that venture capitalists investing in digital pathology may think twice about continuing to do so. Many companies are already in their second round of funding, and the things they were promised – a fantastic market with millions of users and a billion-dollar industry like radiology's – hasn't really come to pass. So when those companies go after another round of investment, the funders may be reluctant if the promise of digital pathology hasn't materialized.

So what can we do? We can use technology appropriately, plan ahead before buying, ensure that we have flexibility, and pay careful attention to what does and doesn't make sense. If we approach digital transition sensibly and for the right reasons, there's a lot to be gained.

In a nutshell...

- **The difference between a "good" and a "bad" digital pathology setup is how well it meets the needs of the laboratory**
- **Telepathology provides the current best return on investment, but there is much to be gained from any digital transition if sensibly managed**

Liron Pantanowitz is Professor of Pathology and Biomedical Informatics and Director of Pathology Informatics, University of Pittsburgh Medical Center, Pittsburgh, USA.

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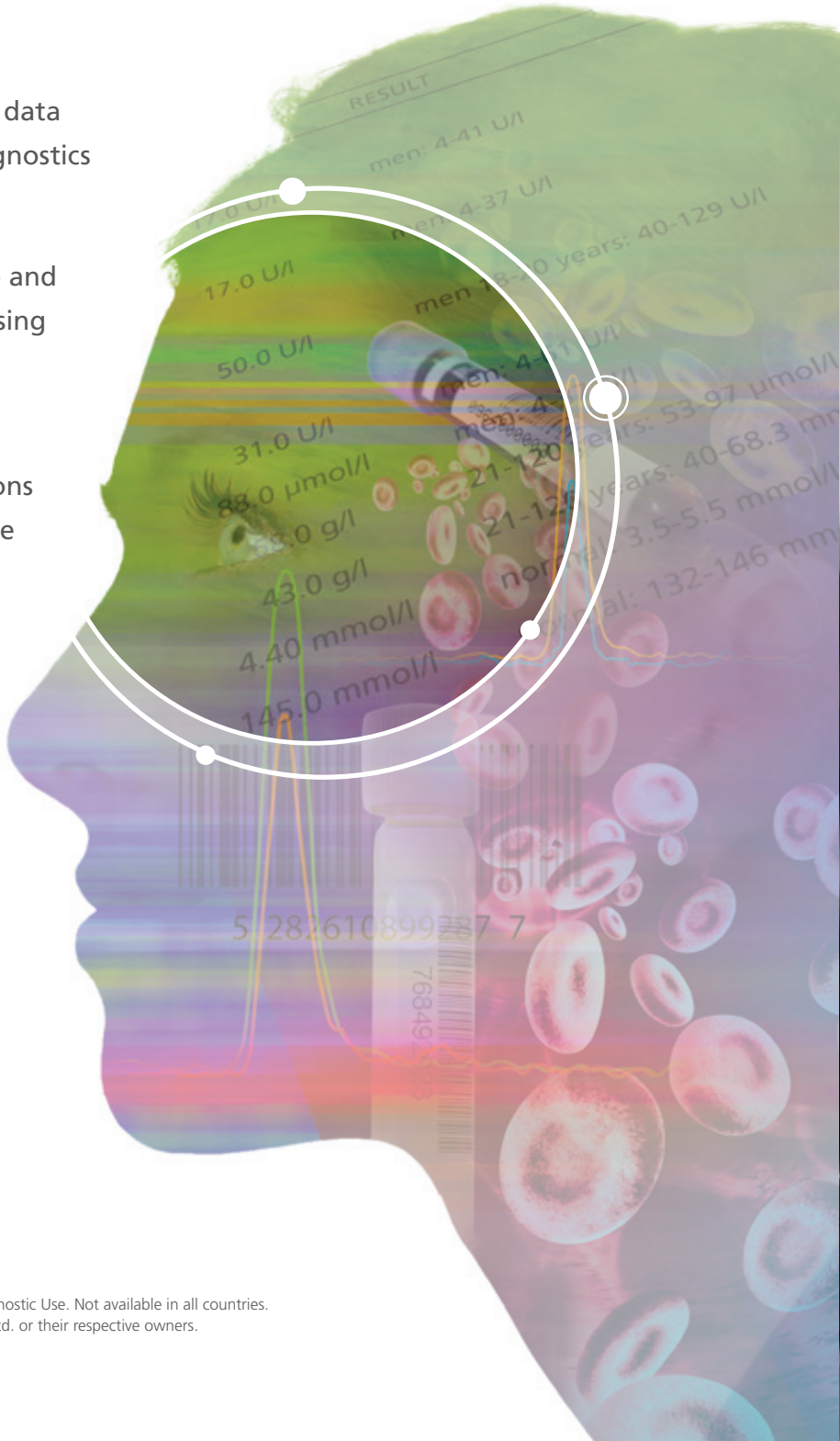

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Strength in Numbers
Using approved protocols for tumor sampling is causing us to lose a lot of valuable information. A simple adaptation to our sampling approach can make a big difference to the accuracy of the diagnostic outcome.

Strength In Numbers

Sampling multiple tumor sites can reveal heterogeneity that would otherwise go unnoticed

By José I. López

When you sample a tumor, what is it you're really looking at? The answer may seem obvious, but what many people don't realize is just how heterogeneous a single tumor may be. What may seem indolent at first glance may in fact turn out to be highly aggressive – but that's something a pathologist might not discover by looking at only a few samples. Unfortunately, that's how a lot of grossing is still conducted. So how can we change this to account for the level of heterogeneity that's often present in cancers? I propose a new approach, which I'm pleased to say has now received good feedback by several internationally-recognized pathologists: multi-site tumor sampling.

At a Glance

- *Sampling a single tumor site reveals what's present at that location – but risks missing high-grade disease due to unevenly distributed heterogeneity*
- *Multi-site sampling can be accomplished affordably if multiple samples are processed in a single cassette*
- *This approach allows pathologists to look at several regions of the same tumor and greatly increases the odds of spotting areas of high-grade disease*
- *Sampling multiple sites requires a greater time commitment, but technology can help – and the added time may be worth it to optimize diagnosis and treatment*

A revealing review

The story started one day in 2012, when I went back to the grossing room to check whether or not a conventional low-grade clear cell renal cell carcinoma (CCRCC) had invaded the patient's renal sinus. I confirmed in situ that it hadn't – but as I was there anyway, I selected a few more samples for microscopic analysis. To my surprise, one of those samples showed some areas of high-grade carcinoma. I had to call the urologist and say, "Sorry; this isn't a low-grade tumor anymore" – the sort of thing clinicians and surgeons refer to as "pathologists' inconsistencies," because they aren't familiar with the complexity of our work.

But that case taught me to ask myself how much important information I was losing by following internationally accepted protocols for tumor sampling. And I did something that might have looked crazy to my colleagues: I began performing prospective total tumor sampling of CCRCCs, so that I could compare the information I obtained that

Histological parameters	*MSTS*	*RS*	*P value (X^2 test)*
High grade (G3/4)	31	21	0.0136
Granular eosinophilic cells	32	22	0.0114
Sarcomatoid phenotype	12	6	0.1
Tumor necrosis	10	7	0.5

Table 1. Comparison between both sampling protocols showing that MSTS outperforms RS. MSTS, multi-site tumor sampling; RS, routine sampling (4).

way with what others got from standard methods. It was a risky decision – not for any medical reason, but because I was at high risk of being killed by my technicians due to the sudden increase in laboratory workflow. But after soliciting the help of some colleagues, I finally got 47 totally sampled CCRCCs… leaving me with over 1,400 slides to review!

"It was a risky decision... because I was at high risk of being killed by my technicians due to the sudden increase in laboratory workflow."

At first, I examined only one slide per centimeter of tumor diameter, as per protocol – but later on, I began reviewing all of the slides. The results were very concerning: while routine sampling detected 7 high-grade tumors in 47 cases, my total sampling detected 17 (1). This means that, when using standard sampling protocols, pathologists may actually be giving incomplete information in their reports. Our methods need to change.

A dynamic disease

Why is this such a problem? Cancer is a dynamic process, and as it evolves, malignant cells develop different mutations in different areas of the tumor. This leads to "regionalization" – unique, stochastic and utterly unpredictable. We still don't know the rules that govern this evolution. In the case of CCRCC, the molecular hallmark is the inactivation of the *VHL* gene, which codes for the von Hippel–Lindau tumor suppressor protein (pVHL). Aberrant pVHL provokes permanent intracellular activation of VEGF, leading to enhanced angiogenesis. Most modern CCRCC therapies are based on anti-angiogenesis – but because of intratumoral heterogeneity, some regions respond to treatment while others don't. The ones that don't are responsible for tumor progression.

Current sampling protocols were designed before we realized that heterogeneity was a major issue. Over the last few years, though, massive sequencing tools have shown us the full scope of the problem… but sampling protocols haven't changed, and new problems require new solutions. The first step in this solution

The Physicist's Story

By Jesús M. Cortés

In the "ideal" situation, where heterogeneity is randomly distributed across the tumor, sampling one large piece of tumor is equivalent to sampling many small pieces. But that's not how it works in real life. Heterogeneity is regionally, not randomly, distributed – and that means the two strategies have obvious differences with very real consequences for patients. To prove it, I used a simple modeling approach to show the clear advantages of one strategy (namely MSTS) with respect to the other (routine sampling, or RS) in detecting intratumoral heterogeneity. The approach we used is the "divide and conquer" algorithm (3), a well-known strategy for solving practical problems in computer science. Briefly, it involves dividing a complex problem into smaller ones that can be solved independently and merged into an overall solution. In this case, that meant revealing the superiority of MSTS as a sampling technique for intratumoral heterogeneity detection.

My main research interests lie in systems neuroscience and neuroimaging – but alongside that work, I will continue to do my best to put experts' intuitions into numbers, just as I've done in this project. Why do I do it? Because I am truly convinced that clinical research can benefit from the methods already well-established in the quantitative sciences.

Jesús M. Cortés is Ikerbasque Senior Researcher and Head of the Quantitative Biomedicine Group at Biocruces Research Institute, Barakaldo, Bizkaia, Spain.

is thorough tumor sampling to learn as much as we can about each neoplasm's individual peculiarities. Because total sampling is impossible in many tumors due to their size, we must choose which parts to analyze – and being as thorough as possible is our responsibility as pathologists. That's where the promise of the multi-site tumor sampling strategy comes in.

"The catch? This was all based purely on common sense."

From my own experience (that is, the crazy study I conducted in 2012), I knew that "the more you sample, the more you find." The question is where to stop. How do you balance finding heterogeneity and establishing a sustainable system? The only way I could envision affordably sampling more tumor regions was to take a higher number of smaller fragments and put several of them on the same cassette for analysis – keeping the total number of cassettes the same, but increasing the number of samples we could examine for the same price. That's what I call the multi-site tumor sampling (MSTS) protocol. The catch? This was all based purely on common sense; I didn't have any objective data to prove that several small fragments from distant tumor regions were more informative than a single large fragment. What I needed to do next was cooperate with a scientist – Jesús Cortés, a physicist who specializes in modeling and data mining (see sidebar, "The Physicist's Story"). Together, we were able to demonstrate that MSTS outperforms routine sampling, and that it does so without incurring extra costs (Figure 1) (2-4).

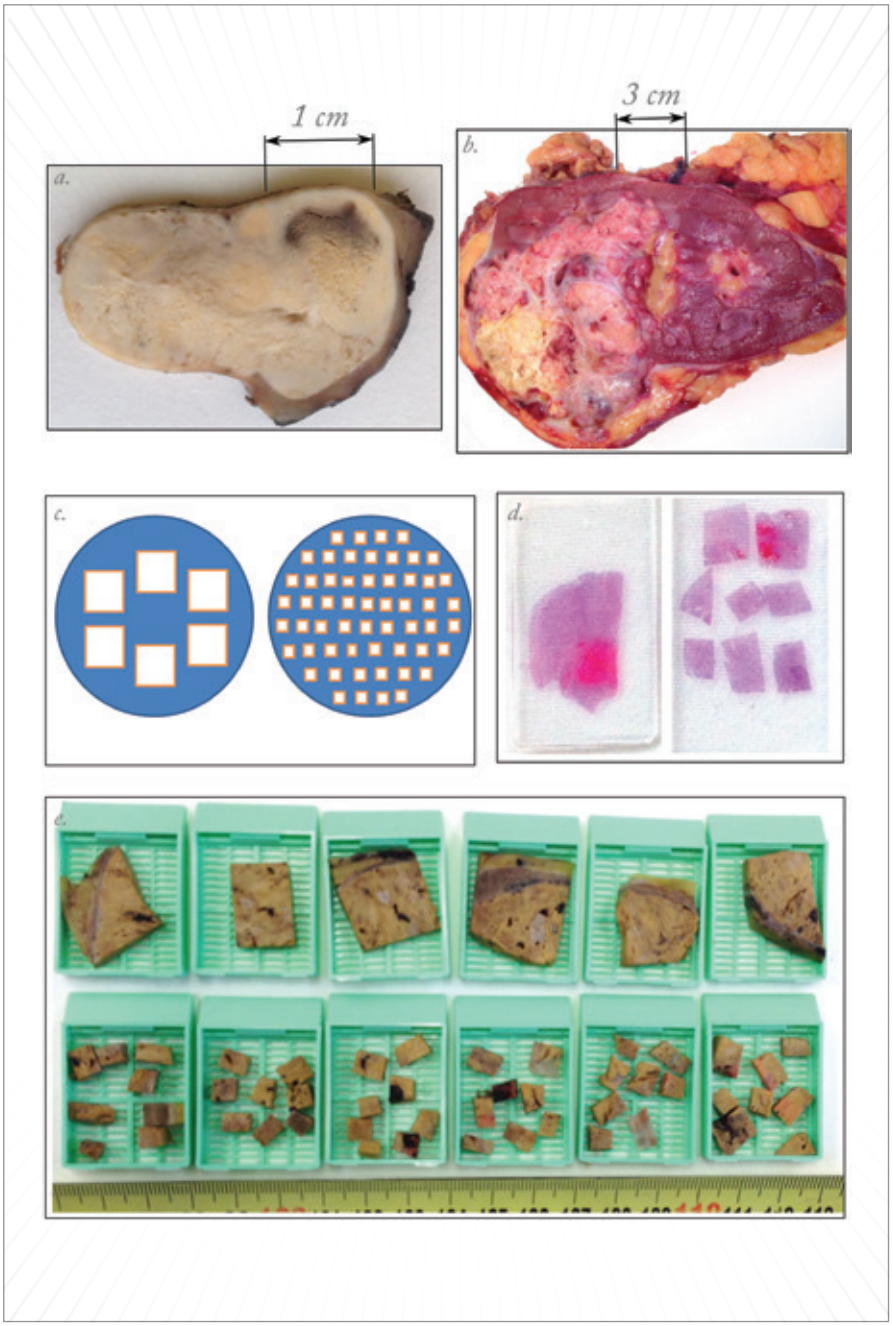

Figure 1. ITH in CCRCCs may be hidden (a) or evident (b) to the naked eye during the management of surgical specimens, an issue that is critical for subsequent tumor sampling. The RS strategy selects for analysis 1 sample per cm of tumor diameter, as reflected at the left side of panels c–d (c, diagram d, histological slide) and at the top row of blocks in panel e. In contrast, the DAC strategy selects more small-pieces for tumor sampling (8 pieces in this example, versus 1 for RS) but the pieces are randomly chosen along the tumor. Importantly, both RS and DAC methods demand the same laboratory costs. ITH, intratumor heterogeneity; CCRCC, clear cell renal cell carcinoma; RS, routine sampling; DAC, divide-and-conquer. Adapted from (3).

The start of a sampling revolution?

MSTS isn't limited to CCRCCs, though; it can be applied to any tumor that can't be sampled in its entirety, and it's especially advisable for neoplasms known to have high intratumoral heterogeneity. We've shown that MSTS is much more effective than routine sampling in detecting intratumoral heterogeneity, and it can easily be combined with molecular testing – but there's a downside: it's also much more laborious for pathologists in the grossing room. That could be a major obstacle to widespread implementation. To overcome this hurdle, we recently proposed the use of a cutting device that significantly reduces sampling time (2). It's important to pave the way for MSTS as much as possible, because I truly believe it's the method we need to use with large tumors to meet oncologists' expectations.

We have already demonstrated in silico that MSTS is more efficient than routine sampling in detecting intratumoral heterogeneity (3). Now we have finished the first clinical validation of our protocol, based on the evaluation of classic histopathological parameters – and the results confirm our expectations. In fact, MSTS detected a significantly higher number of tumors with high-grade areas in a series of 38 CCRCCs, even though the speed, quality and cost of the two techniques are comparable (Table 1) (4). Right now, we're developing more clinical validations of the method, so we're looking forward to even more interesting data by the end of the year.

Adoption couldn't be simpler

We're now using MSTS routinely in our own laboratory, because it has proven to be so advantageous in large tumors. How can other labs adopt our method? It's fairly straightforward: when making the paraffin block, simply put six to eight tissue fragments in the same block instead of only one – not a big change, and the only difference between routine sampling and MSTS! I hope that the method's simplicity and its benefits will convince other pathologists to consider it, but I know that will take some time.

My advice to others is to seriously consider whether or not you're really optimizing your own work. If you aren't, make the changes needed to benefit your patients as much as possible. I think we have developed somewhat of a contradictory attitude – making microscopic and molecular studies our most important goal, considering the macroscopic analysis of tumors a secondary task, and leaving fundamental work like tumor sampling to the residents. We need to return our attention to those aspects of our work, and to update our most basic protocols. Keep in mind that the success of our expensive and sophisticated devices depends on a single, humble decision: how much tumor must I sample, and in what way, to efficiently detect intratumoral heterogeneity?

José I. López is Head and Professor of Pathology at Cruces University Hospital, University of the Basque Country, and Senior Researcher at Biocruces Research Institute, Barakaldo, Bizkaia, Spain.

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40–43
A Patient is More Than a Price Tag
Genome-wide sequencing is highly valuable in providing a timely, definitive diagnosis of intellectual developmental disorders, as well as of other conditions, but for it to succeed, collaboration between a multidisciplinary team that includes the pathologist is needed.

A Patient Is More Than a Price Tag

In patients with intellectual and metabolic differences, genome-wide sequencing can provide diagnoses and even potential routes to treatment

Michael Schubert interviews Maja Tarailo-Graovac and Clara van Karnebeek

Intellectual developmental disorders (IDD) are both prevalent and burdensome. With one in 40 people affected – and often experiencing additional symptoms like epilepsy or behavioral disturbances – IDD results in significant social and economic costs, making identifying and treating as many as possible a major goal. But with hundreds of known disorders and an estimated 95 million patients with cases of unknown cause (1), how can we take on the task of diagnosing the exact cause of IDD?

We know that many inborn errors of metabolism (IEMs) – monogenic defects causing enzyme deficiencies that result in energy depletion and toxin accumulation – can cause altered intellectual development. In cases where the error can be treated (for instance by medical diets, vitamins or medications), we see improvements not only to development, but also to psychiatric, neurological and systemic health. In an attempt to bring these benefits to as many IDD patients as possible, we investigated the diagnostic potential of genome-wide sequencing – and hit the jackpot. Of the 41 families enrolled in our study, all of whom experienced IDD and metabolic changes due to rare mystery conditions, we were able to identify the precise genetic causes in 28. We also discovered 11 new disease genes and several new phenotypic manifestations of previously known disorders (2). Most importantly, in four out of 10 cases, knowing the diagnosis allowed us to start treatment that improved their daily lives and health. It's a wonderful start to large-scale DNA investigations of IDD, and one we anticipate expanding upon in years to come – because the more we can learn about the genetics of brain function, the better placed we are to change the lives of patients and families dealing with IDD.

At a Glance

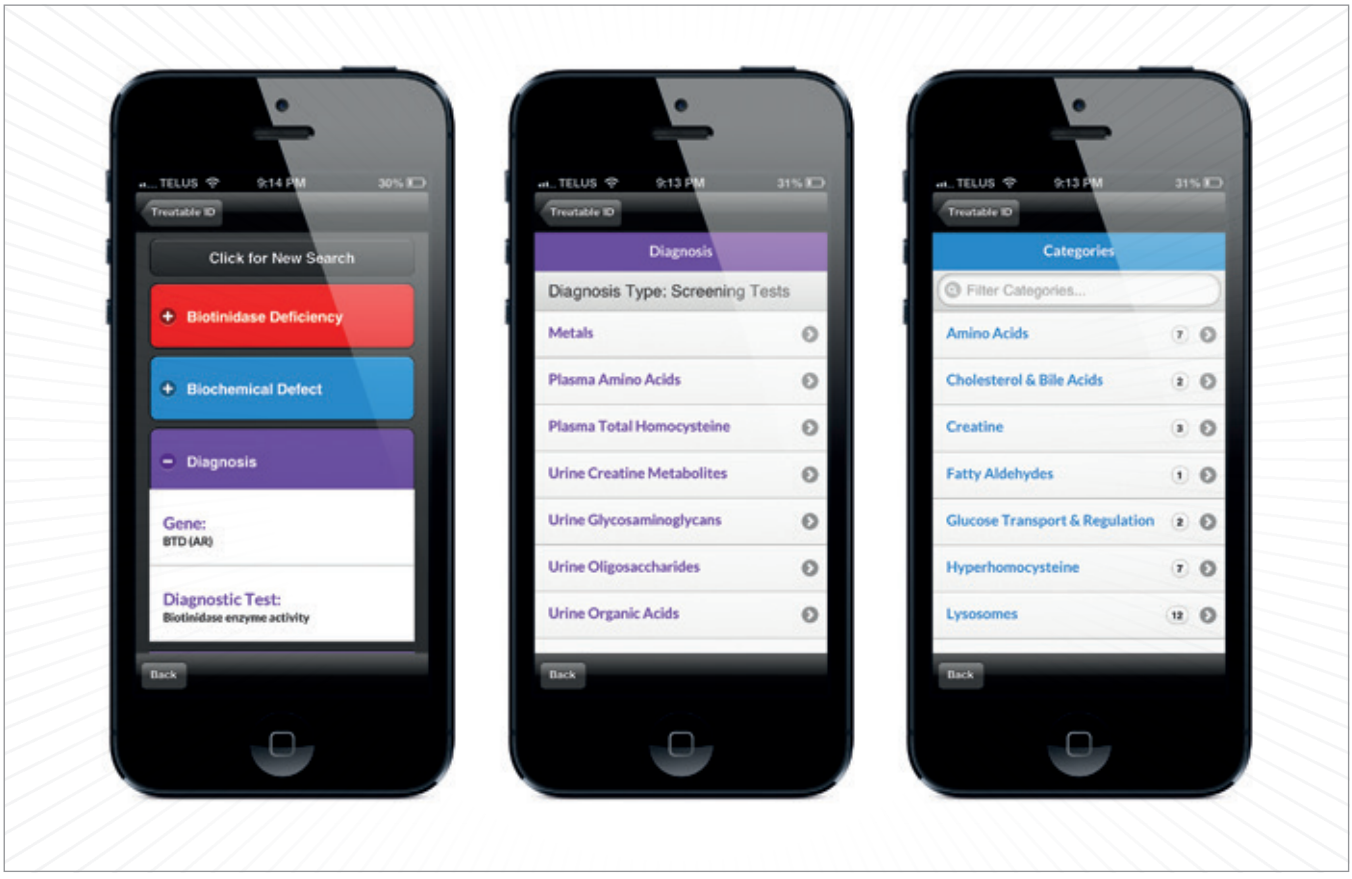
- *Intellectual developmental disorders (IDD) are prevalent and burdensome – but those caused by inborn errors of metabolism can often be treated if diagnosed using techniques like genome-wide sequencing*
- *An initial study applying whole exome sequencing resulted in diagnoses for 68 percent of participants, as well as identification of new genes and disorders*
- *In a subset of these patients, diagnoses allowed for targeted treatments to improve developmental and health outcomes*
- *Genomic sequencing holds promise for IDD and other conditions, but researchers, pathologists, clinicians, bioinformaticians and patients must work together for it to succeed*

Selection strategy

The focus of our work was on patients with both IDD and biochemical or metabolic abnormalities, because the combination is suggestive of a genetic cause that is potentially amenable to treatment. We call those inborn errors of metabolism. Our patient selection criteria for genome-wide sequencing included either confirmed IDD or a strong indication of future IDD development, as well as a metabolic phenotype of unknown origin. Because ours is a research-based study focused on discovering novel rare genetic disorders and clinical manifestations, another important patient selection criterion was that previous genetic and biochemical (deep phenotype) testing done in a clinical setting had been elaborate, but had not yielded a diagnosis. In our cohort of patients, the underlying genetic defects were mainly due either to novel genes or to known genes with novel phenotypes – confirming that our patient selection criteria are useful for enriching gene discovery.

> *"Genome-wide sequencing offers efficient and timely profiling of patients' whole exomes and genomes – and, with exquisite data interpretation, can yield a definitive diagnoses."*

But one thing that may be too easily forgotten is that good research isn't the only marker of success. For our patients and their families, early diagnosis is of paramount importance to ensure they receive the right treatment at the



Screenshots of the Treatable-ID app.

right time. And not just that – it also provides an answer and a prognosis, avoids unnecessary further testing, and enables accurate genetic counseling. Genome-wide sequencing offers efficient and timely profiling of patients' whole exomes and genomes – and, with exquisite data interpretation, can yield a definite diagnosis in a very timely manner. In our opinion, any child with IDD deserves a thorough workup, including a chromosome microarray and Treatable Intellectual Disability Endeavor (TIDE, tidebc.org) first-tier metabolic testing. If those tests are negative – or if the patient needs a diagnosis faster than they can deliver one – then we think it's entirely warranted to use genome-wide sequencing as a first-line test. That's easier said than done, because availability is still an issue, but we believe that every patient deserves access to whatever diagnostic tools are needed. Of course, not every patient will receive a diagnosis; at the moment, about half will remain undiagnosed even with genome-wide sequencing, but as knowledge and expertise grows, these numbers will change for the better.

Winning the cost argument

An "ideal" patient for exome sequencing is one with a suspected rare monogenic disorder for whom thorough clinical phenotyping data is available. In our work in particular, we focus on whole exome sequencing (WES) in patients with unexplained IDD and metabolic phenotypes of likely genetic origin. Whole genome sequencing (WGS) has an even broader target population, because it's also capable of revealing copy number variants. What do all of these tests have in common? They can't occur in isolation – experts must be available to help analyze and interpret the bioinformatics findings. Too many patients receive test results they don't understand, and even the doctors ordering the tests may lack the specialist education to explain the results fully. Patients should never be provided with genetic information without the guidance to help them understand its implications.

Of course, expertise can cost money – and when a test requires close collaboration between several members

Simplifying Sequences: Treatable-ID

By Maja Tarailo-Graovac and Clara van Karnebeek

We have developed an app for clinicians called Treatable-ID (treatable-id.org), which we hope will enhance early diagnosis of treatable inborn errors in patients with IDD. The app provides information on the different IEMs and allows users to search by signs and symptoms – useful for narrowing down the differential diagnosis and fine-tuning second-tier testing on the TIDE protocol. It can be used in two ways: either to scrutinize the WES/WGS data for variants in the encoding genes during bioinformatics analysis or to identify the biochemical test of choice for a given variant. Right now, we're seeing hundreds of users – from trainees to specialists – on the app's website every day, and over 8,000 downloads per year worldwide. It's even used in the American Board of Medical Genetics and Genomics teaching curriculum! As we discover new treatable diagnoses, we plan to keep Treatable-ID updated so that it's always a complete, easily accessed resource for healthcare providers.

of a multidisciplinary team, it's easy to question whether or not it's cost-effective in the clinic. In our experience, the price tag on genome-wide sequencing is only about one-tenth of the total cost of the diagnostic odyssey – but the benefit can be greater than that of any other expenditure. Patients and families are better-placed than anyone else to see how the speed and timeliness of sequencing impacts diagnosis and patient management, especially if we're then able to treat the disease in question. For them, it's life-changing, and that simple fact makes the test worth the cost.

A genomic journey of discovery

In our study's cohort of IDD patients, we identified 11 novel genes implicated in human disease, and from that starting point, we were able to define several new disorders. For instance, we identified a form of hyperammonemia due to carbonic anhydrase VA deficiency in patients with defective *CA5A* genes – a deficiency amenable to treatment with carglumic acid and an emergency protocol (3). We also discovered epileptic encephalopathy due to N-acetylneuraminic acid phosphate synthase deficiency, and showed using model organisms that this deficiency is amenable to treatment with early supplementation of sialic acid, a sugar present in breast milk and other food products (4). And what of the other nine genes? Thus far, we've been able to ascribe to them two novel, potentially treatable disorders due to *GOT2* and *ACACB* deficiencies, as well as seven candidate novel disorders.

The current best estimate for the total number of rare genetic disorders is approximately 7,000 – though the true number may be a bit higher (and only a subset of these are neurometabolic diseases). Given that as many as an estimated 50 percent of genes underlying known Mendelian phenotypes are still unknown, we anticipate that, in coming years, many more new disorders will be uncovered using genome-wide sequencing. As a matter of fact, we're already working on that – the number of patients we have analyzed using this technology since publishing our initial study findings has tripled, and so have the discoveries we've made. Understanding the pathways and disease mechanisms for both metabolic and non-metabolic genetic conditions is important – it allows us to explore new treatment options, something that is already happening for conditions like Rett syndrome, Fragile X syndrome, and tuberous sclerosis.

We aim to continue discovering novel neurometabolic diseases using genome-wide sequencing, but we hope to place more focus on WGS rather than WES now that we're approaching the era of the US$1,000 genome. We'll also be expanding our novel gene discovery approach further to include other neurodevelopmental conditions like atypical cerebral palsy. Not only that, but we're hoping to move into multiple –omics technologies (like transcriptomics and epigenomics) to identify genetic modifiers and better understand the phenotypic variability in patients with rare metabolic disorders. Ultimately, we hope that this combination of approaches will improve patient management, increase the predictability of disease outcomes, and help us to identify metabolic targets for future treatment.

Collaboration in the clinic

How might genome-wide sequencing change the clinical laboratory's day-to-day routine? We think it's already doing so – and that the changes will keep happening. Single tests will slowly disappear as sequencing takes their place; it's an ongoing process for monogenic diseases, but in the future, we expect the same for polygenic and multifactorial diseases. And genomics can impact more than just diagnosis and counseling; four out of 10 patients can receive treatment tailored to the underlying condition once identified (2)! As genetic analysis assumes an ever more critical role, teamwork between pathologists, bioinformaticians, clinicians and genetic

Testimonials from users of the Treatable-ID app (see Sidebar "Simplifying Sequences: Treatable-ID").

counselors will be key for success. This is truly "big data," and the more conditions and secondary findings we encounter, the more complex and challenging it becomes. We need well-informed, collaborative interpretation of that data, and we need to ensure that vital phenotypic information isn't overlooked in our eagerness for genotypic data. In short, we need smart –omics!

That's the key message we want to send to pathologists and laboratory medicine professionals working in the IDD field: that it's vital to have close collaboration between experts in multiple disciplines in the era of –omics medicine. We attribute the success of our approach to efficient and extensive communication between the physicians who performed the deep phenotyping, the bioinformaticians who developed a semi-automated gene discovery pipeline and performed data interpretation, the laboratory scientists who performed experimental validations, the clinicians who developed improved treatment strategies based on our diagnoses, and – of course – the patient and family affected by the disorder. With this collaborative, multidisciplinary approach serving as a model, the future of genomic medicine is bright!

Maja Tarailo-Graovac is a research associate in the Wasserman laboratory at the University of British Columbia's (UBC) Centre for Molecular Medicine and Therapeutics (CMMT), Vancouver, Canada.

Clara van Karnebeek is a principal investigator at CMMT and an Assistant Professor in the Division of Biochemical Diseases, Department of Pediatrics, at the UBC's Faculty of Medicine.

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46–49
Inside Industry
Companion diagnostic tests come with their fair share of friends and foes in the pathology community. But what is it like to be a pathologist involved in their development?

Inside Industry

The pathologist's perspective on developing a companion diagnostic

Nick Miller interviews Bharathi Vennapusa

What does it take to create a competitive companion diagnostic? Bharathi Vennapusa outlines her role in the development and approval of the ALK CDx – a fully-automated immunohistochemistry assay that identifies lung cancer patients who may be eligible for treatment with crizotinib.

How did you get involved in companion diagnostics development?

After training as a pathologist and specializing in molecular pathology, I decided I wanted a career that was neither entirely basic research nor clinical practice. I didn't know much about companion diagnostics at that time, but through a friend I learned about Ventana Medical Systems (now a member of the Roche Group), which was active in the field. Pathologists often don't consider careers in pharma, but I became inspired by the prospect after reading a journal article by Ventana's Chief Medical Officer, Eric Walk, which discussed the role of pathologists in the industry. I decided I wanted to get involved, so I joined Ventana as a pathologist in companion diagnostics.

The role allows me to get involved in research that can be translated into clinical practice. Certainly, our biomarker assays can be used for research, but our main goal is to develop assays that can be used in the clinic. We all have our own reasons for joining the company – some may have family members afflicted with cancer, for example – but we all share a real personal interest in improving the lives of cancer patients. In reality, companion diagnostics are the cornerstone of personalized healthcare; they are critical to finding the right treatment for the right patient.

Why develop ALK CDx, given that a competing product was already available?

It's true that Abbott was already marketing the Vysis fluorescence in situ hybridization (FISH) assay as a companion diagnostic for Xalkori (crizotinib). But Pfizer wanted to develop an immunohistochemistry (IHC) assay for the same drug, and so they approached us. From my perspective, having worked with both FISH and IHC assays, I can say that IHC has substantial advantages. The full automation of IHC makes it more efficient versus FISH – patients can receive results in days compared to weeks, which is an obvious plus. The more complex set up required to read a FISH assay also makes it more expensive when compared with IHC, which can be read by any trained pathologist with a regular microscope in a regular setting.

"After training as a pathologist... I decided I wanted a career that was neither entirely basic research nor clinical practice."

Based on our validation studies, the quality of data between the two assays is comparable.

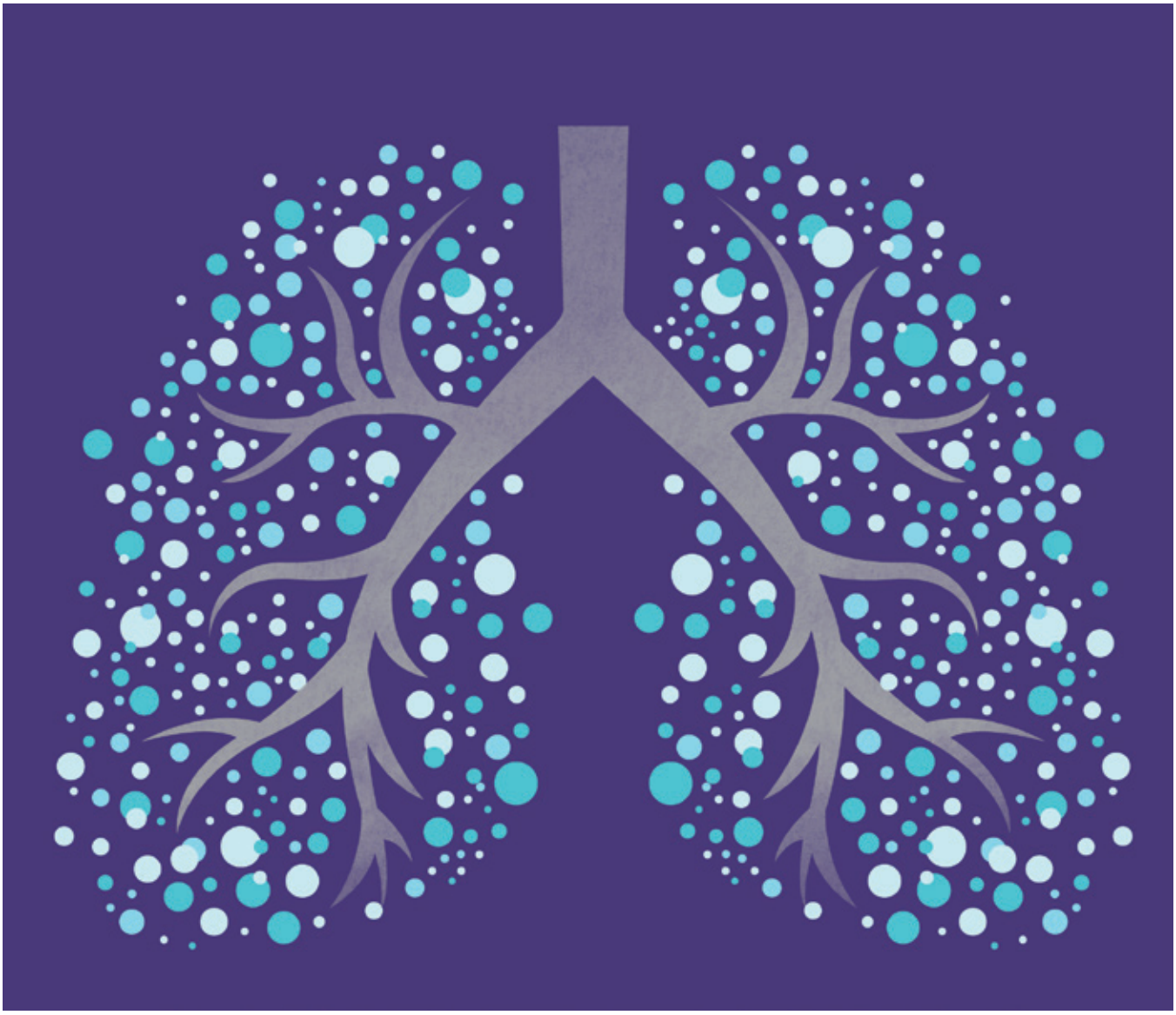
How straightforward was the regulatory pathway?

We have found the FDA to be very helpful during product development, both with diagnostics and with drugs, and it was the same story for the ALK CDx assay. I think the encouraging data associated with new cancer immunotherapies is helping regulators rethink their strategy and guidance, which is also making them increasingly more collaborative – especially with regard to relevant companion diagnostics. Indeed, the FDA encourages diagnostic and drug companies to collaborate on strategies to exploit the many molecular markers that have been discovered. It's a regulatory attitude that is likely related to the many unmet medical needs in oncology; at present, only a minority of cancers are treated with targeted therapies. Regulatory support for the development of companion diagnostics will help get new targeted treatments to cancer patients sooner rather than later.

All the same, when ALK CDx was approved, we all felt like a great

At a Glance

- *A career in industry can be hugely rewarding for pathologists, especially with the rising interest in companion diagnostics*
- *Working to develop the ALK CDx assay, Bharathi Vennapusa explains how regulators are rethinking their strategy to encourage personalized therapy and diagnostic approvals*
- *Challenges remain to developing a good companion diagnostic, though, including difficulty in procuring tissue and reimbursement*
- *But there continues to be substantial growth in the field which, in the future, is likely to see more multiplexing and digital solutions*



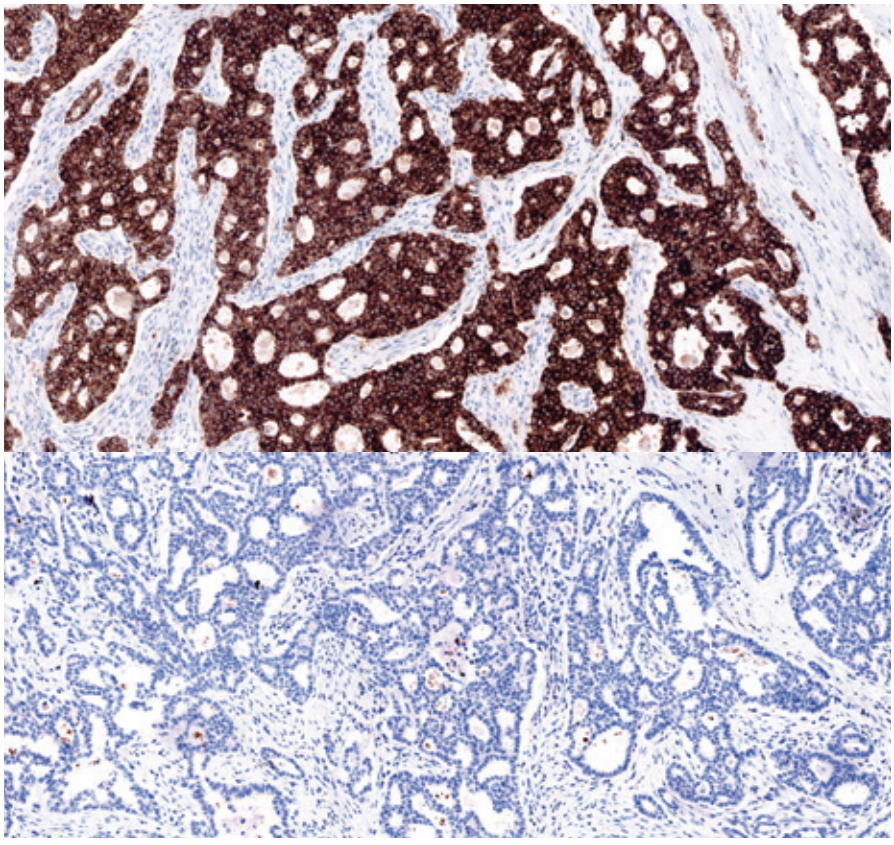
milestone had been achieved. Everyone was excited – not just the internal team, but the entire company – because developing a good, sensitive and specific assay takes a lot of work, and submitting documentation and answering the questions posed by the regulators can be stressful. The approval was great in itself, but it also gave us confidence in our other development-stage companion diagnostics.

What challenges did you encounter?

One of the major challenges facing all companion diagnostics companies is the difficulty in procuring sufficient cancer tissue for product development. Validating the assay requires many tests and studies, which was particularly challenging because the prevalence of ALK+ lung cancer is about five percent. We had to screen thousands of patient samples to get sufficient numbers to support our ALK CDx assay development program, and it's not always easy to get good quality samples in these quantities.

Another challenge is that, although the ALK CDx assay is very easy to interpret, pathologists still need to be trained in its use so that they can appreciate the nuances of the assay, and understand its constraints. Essentially, we need to do everything in our power to prevent the

"I'd really like payers to develop a better understanding of what we are doing. I'd also like the medical community to better appreciate what pathologists do."



Positive (top) and negative (bottom) case of lung tissue stained for ALK with Ventana ALK (D5F3) CDx Assay.

risk of a wrong diagnosis. To that end, we developed an e-learning tool for the ALK CDx assay to walk pathologists through the challenges that they might encounter when interpreting the assay in real life. Such training is an area that we intend to continue to work hard on and constantly improve.

What changes would you like to see in the companion diagnostics industry?

One of the greatest opportunities for change lies in the economics of companion diagnostics. At present, diagnostics are not always reimbursed – and when they are it is at a much lower rate than the related therapeutic. This holds back funding for diagnostics development. I'd really like payers to develop a better understanding of what we are doing. I'd also like the medical community to better appreciate what pathologists do. Pathologists are the ones enabling the diagnosis, and the tests pathologists do determine what treatment the patient will receive. Companion diagnostics essentially help the patient find the right treatment, which also means reducing the risk of exposing the patient to unnecessary treatment. Yet the funding for companion diagnostics development, and the incentives for commercialization, are relatively low. We need to educate key stakeholders about the value of these products – not just pathologists, but also payers, government bodies and private insurance companies.

I'd also like to see an honest dialog between stakeholders, including the regulators, around the issue of obtaining sufficient cancer tissue to validate companion diagnostics. I feel that there is room for improvement in that area. In fact, communication in general is an area for constant improvement. We certainly have a close relationship with the regulatory bodies in the US, China, and Europe, but we want to improve and extend that further. Likewise, I also think we need to continue to grow our relationships with pharma companies and with independent pathologists. Getting feedback from experts outside the company – for example, on how we can improve training in assay interpretation – is critical. We've learned a lot of lessons from the ALK CDx assay, which we've already started implementing in the development of newer companion diagnostics.

Any thoughts on the future of companion diagnostics?

Over the last four years I've seen explosive growth in companion diagnostics development. There were only one or two projects when I started, but now we are working on more than 10 at any one time.

In all our companion diagnostics

projects, especially the IHC-based assays, we expect to see more success, but also more assay complexity. For example, while some drugs may be safe and effective when prescribed on the basis of assaying a single biomarker, in the future we may need to base a prescription on two or more biomarkers, which implies presentation in a multiplex format. Accordingly, we are developing a multiplexing capability that can test for multiple markers on a single slide. This resource may also help address the difficulty in procuring sufficient tissue specimens from cancer patients, which is being exacerbated by the trend to use less invasive procedures. So if, as seems likely, diagnostics developers have much less tissue to work with in the future, next-generation technologies like multiplexing may be essential to be able to fully exploit what is available. In addition, we may need to develop digital pathology techniques, PCR, next generation sequencing, and bioinformatics tools to help decipher the data output.

By expanding the use of new, relevant technologies in companion diagnostics, by incorporating additional guidance from regulatory agencies, and by closely collaborating with regulators, drug developers and diagnostic companies, I believe society will quickly start to see the benefits of next generation companion diagnostics. And I am very excited to be part of this evolving story.

Bharathi Vennapusa is Director Clinical Operations at Ventana Medical Systems, Tucson, USA.

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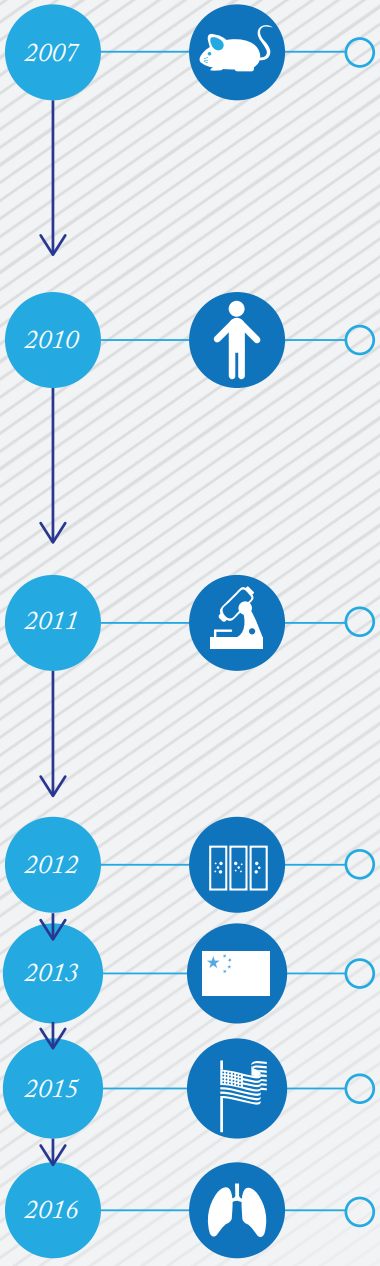
Timeline: Crizotinib and Companions



Trials and Transplantations

Sitting Down With… Alejandro Madrigal,
Scientific Research Director at
Anthony Nolan, London, UK.

How did you become interested in pathology?

When I was a teenager, I dreamed of becoming a doctor. It was a difficult time; my life had changed suddenly with the death of my father and I had to work at many different jobs to support my family. I ended up falling in love with medicine and eventually I graduated from the Universidad Autonoma de Mexico (UNAM) and specialized in internal medicine. Then my life changed again – I was accepted at Harvard University for my clinical training, received a World Health Organization fellowship and spent four years studying immunogenetics at the Dana Farber Cancer Institute. But the changes didn't stop there; my next move was to London, where I researched human leukocyte antigen polymorphisms and trained at Imperial College London and University College London, and then I moved to California to undertake a postdoctoral position at Stanford. It was in 1993 that I accepted the position of Scientific Research Director at the Anthony Nolan Trust, a post that has served me in good stead for the past 23 years, and has allowed me to contribute substantially to the area of hematopoietic stem cell transplantation (HSCT). What have I learned from studying pathology around the world? That medicine is a universal subject with one common goal: to help patients survive and improve their quality of life. Resources may make a difference to the quality of medical care, but we all just want the opportunity to cure every patient in need of treatment.

What are you most proud of in your career?

The Anthony Nolan Trust was established in 1974 by Shirley Nolan, whose son Anthony had been diagnosed with Wiskott-Aldrich Syndrome. At that time, there were no other registries and the concept of being an unrelated donor did not exist. Shirley Nolan changed the world, and thanks to her brilliant initiative, there are now over 28 million registered donors worldwide and over one million transplants have been performed. I am very proud to have established the Anthony Nolan Research Institute (ANRI), which has published over 1,200 scientific papers with over 12,000 citations. We've also become a center for education, training over 160 scientists, and have helped communities abroad to establish and develop their own registries. The ANRI has collaborated on a global scale to improve the outcome of HSCT and this has been a great satisfaction to me.

I feel strongly that my involvement in teaching and training is one of my greatest achievements. We owe a responsibility to the younger generation – to give them a varied education and to help them progress in their careers. I feel that dedicating our time to opening new ways of thinking, providing new opportunities, and leading our students down the road to knowledge pays us back enormously in many different ways.

What are the most interesting projects you've worked on?

I led the "AlloStem" Consortium, which brought together clinical and research groups from across the European Union and beyond. Over 100 scientists and 24 biomedical research teams joined our Associate Membership program, and five small- and medium-sized enterprises worked on developing immunotherapeutic strategies to treat hematological and neoplastic diseases. The results from the project were very impressive – with over 288 papers published, 17 patent applications, and four new databases created, I think the work will generate important contributions to the field of stem cell transplantation for many years to come. Currently, I co-coordinate a follow-on project: "T-Control," a consortium of six leading European groups that use immunotherapeutic strategies to generate cell therapies for graft-versus-host disease, leukemia and post-transplant infection complications. We are already initiating clinical trials and are enthusiastic that, with the development of new cell therapy weapons, we may be able to control most of the complications that affect the outcome of HSCT.

And your hopes for the future?

I hope that we'll be able to control or even cure cancers without the need for HSCT and that we'll be able to generate alternative treatments. We are already seeing pioneering steps being taken, such as chimeric antigen receptor T cells, PD-1 antagonists and targeted drugs. I'm optimistic that the stem cells can be applied to other conditions, too. In the shorter term, with over 28 million donors registered and new developments in transplantation all the time, I want every patient in need of HSCT to be able to find a donor.

Over the next few years, my research group plans to use third-generation sequencing and other new technologies for genotyping, with the goal of demystifying the role of immunogenetic differences in HSCT outcomes. We also want to develop new cell therapy strategies using cord blood cell products, such as natural killer cells, regulatory T cells and cord plasma to fight relapse, infection and graft-versus-host disease. We're hoping to coordinate clinical trials in these areas very soon!

What advice would you give to a young Alejandro Madrigal?

To always work with passion in the hope that you can make a difference – however small – to the lives of patients, as this would be a wonderful contribution to improving the health of as many people as possible around the world. I think that all pathologists should do their jobs with passion, because the ultimate goal is to change and improve clinical practice, save lives, and make the world a better place.

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