The Future Development of Digital Pathology Technologies, Implications for Pathology Labs and the likely FDA Regulatory Responses

Commentaries from the Digital Pathology Congress

Global Engage
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- Stephen Schmechel, Associate Professor, Chief of Pathology (Acting), Harborview Medical Center, Department of Pathology, University of Washington School of Medicine
- Tom Quick, Product Specialist, Carl Zeiss Ltd.
- Olga Colgan, Director Commercial Marketing, Aperio ePathology, Leica Biosystems
- Dr Madhuri Warren, Managing Director, Pathology Diagnostics Ltd
1. The Future is Digital

The continuing growth and advances in digital pathology solutions are transforming the industry. With wide ranging applications and benefits including: reduction in lab costs; increased workflow efficiency; greater interconnectivity; effective training / education methods; and improved decision making are enabling enhanced patient care. The result is that Digital Pathology is rapidly gaining momentum worldwide.

Allied Market Research, the global market research and business consulting wing of Allied Analytics LLP based in Portland, Oregon issued a report which predicted that the global digital pathology market will be valued at $5.7 billion by 2020.

Paul van Diest, Head of Department, Professor in Pathology, University Medical Center Utrecht, Netherlands is also cautiously optimistic. When asked to look into his crystal ball he said that “It’s not so easy to predict what’s going to happen over the next 5 years. We started [introducing digital pathology to our hospital] 6 years ago, and it didn’t go as fast as I predicted then! So I have to be a little bit moderate, but I see that digital pathology is pretty much on the verge of a breakthrough. There is so much interest, no longer just in academic hospitals but also in a lot of regional hospitals … [So] I would dare to predict…that in 5 years’ time, this will be a fairly established piece of technology at least in the Western world, and … I really think we’ll see a breakthrough in clinical practice of this technology.”

Keith Kaplan, Pathologist, Charlotte, NC, USA, with 15 years’ experience of observing the arrival of digital solutions for pathology thinks that the technology is at a tipping point in terms of adoption. In his view the market worldwide is expanding due to the need for efficiencies and workflow given changes in healthcare. The wider adoption of use of digital pathology is predictable because it provides pathologists with more tools in their toolbox to provide better care and improved outcomes. He says “I think these enabling technologies will help all of us deliver better care more efficiently.”

Keith does not predict the end of light microscopy – it is he says “an adjunctive tool to conventional light microscopy techniques, histopathology techniques that pathologists worldwide have done for 150 years.”
2. Drivers for Growth

One of the clear drivers towards the adoption of digital pathology is the potential cost savings to whole health systems, if not pathology labs, which will be confronted with the upfront costs of adopting the technology. Efficiencies in workflow and the use of resources are clearly identified in the NHS England document Digital First: Clinical Transformation through Pathology Innovation as one of the benefits of the technology. But equally important are patient outcomes.

Liron Pantanowitz, Associate Professor of Pathology & Biomedical Informatics, Director of the Pathology Informatics Fellowship Program, University of Pittsburgh Medical Center thinks that the adoption of digital pathology in healthcare is driven by both cost savings and also patient outcomes. He says “Cost savings ultimately will be shown through productivity and better quality ... there will be a return on investment for purchasing and using digital pathology systems.” On the other hand he says by “facilitating the sharing of cases so that the right case is seen by the right pathologist with expertise in that area, particularly helping underserved areas, the patient outcomes will be improved through better accuracy and more reproducible diagnosis with the aid of computer-assisted tools that will be available with digital pathology.”

And improved Patient outcomes are the name of the game. Han van Krieken, Full Professor, Head of Department Pathology, Radboudumc Nijmegen, The Netherlands and President of the European Society of Pathology gives a practical example of a routine situation when a patient presents with a very specific problem like a brain tumour or a child who has an aggressive tumour on a Saturday. It is unlikely that the specialized pathologist will be in the hospital. Even today in this situation digital pathology can produce an image for a specialist to review at home on a laptop or iPad.

And NHS England? In their report Digital First: Clinical Transformation through Pathology Innovation it foresees benefits ranging from personalised medicine, integration with mobile telephones and transforming the treatment of patients in terms of maintaining health rather than managing disease.
3. Obstacles to the Adoption of Digital Pathology

Liron Pantanowitz thinks that firstly, pathologist are only going to give up light microscopes and adopt a whole-slide imaging device if they can be shown how that instrument can enable them. He says that “there are lots of benefits but I don’t think pathologists realize what all those benefits are. There are benefits to being mobile. There are benefits to the added information and image analysis that can be performed on an image, computer-aided diagnosis, and just basically if you can show a pathologist that it’s far easier to move an image around than it is to move a patient or actually themselves move around, I think they will be willing to surrender their microscope and adopt digital pathology.”

Peter Hufnagl, Head Digital Pathology & IT, Institute of Pathology, Charité University Hospital Berlin, Germany observed that the current state of digital pathology is currently “a little bit complicated.” While it is possible to enumerate the clear advantages of digital pathology and to predict a revolution in pathology labs, it is clear that the solutions being offered are not all on a level. This, he says, means that “sometimes pathologists are a little bit frustrated about the real solutions, which they get in their hands, especially in the context of clinical pathology.”

For example, the loss of particles during the scan of a scanning system is sometimes very critical because one particle in a total slide may be a tumour particle, and if you lose this particle it can be critical for the patient. Peter also thinks that, in the case of diagnostic pathology, the workflow of virtual microscopy has the potential to run efficiently but just at the moment this is not really the case. However, he concedes that if you look at other fields, which are part of clinical pathology especially for instance measurement of mark-offs that support a diagnosis, virtual microscopy runs quite well and delivers—especially in quality.

With a word of warning for labs adopting digital solutions, Peter says you must “test and test and test.” There are several systems and interfaces for a lab using virtual microscopy and scanning microscopy and these interfaces are sometimes open. On the other side, you have processes which are run in the laboratory by humans. Understanding the way everything works and how changes in one area will affect outputs is in his view essential.

3.1 Validation

Dr Madhuri Warren, Managing Director, Pathology Diagnostics Ltd., commenting on the Digital Pathology Congress, said “I think the take-home message […] is that validation of image analysis platforms is absolutely vital. We’re cannot get away from having trained scientists and more importantly pathologists providing the ground truth for what biomarker assessment should be and from which we can actually validate the algorithms that we use in the clinical setting. I think there’s a lot of development and scope for evolution of the image analysis platforms.”

3.2 Pattern Recognition

Alison Bigley, Associate Principal Scientist, Investigative & Translational Pathology, AstraZeneca, UK argues that pattern recognition in digital pathology was valuable because it offers a new support role to the diagnostic arm of the pathologist, “to remove the obvious bias that we have, which is inherent in regional analysis in selecting our regions of interests and features that we want to characterize and classify. This supports the pathologist in ensuring that we have robust data.”
The use of pattern recognition is really in its infancy, so researchers are trying to understand how they can apply pattern recognition and what value this really adds to pathology as a whole. The potential for the future is that pattern recognition alleviates the laborious interactive processes, so that work can be targeted to other areas rather than spending too much time on the sort of minor problems within samples.

However, the robustness of validation with regards to pattern recognition is “really quite an novel and challenging area for us in that we don’t have a dedicated validation process as such,” says Alison. “We’re trying to use sort of areas, which can determine the accuracy of the pattern recognition we’re using by looking at fitness curves and receiver operating characteristics in order to provide a knowledge and a degree of accuracy that people can actually relate to and ensure that they’re going to generate again robust data in support of their tumour classification and tissue classification.”

3.3 Learning Phase

Han van Krieken, Full Professor, Head of Department Pathology, Radboudumc Nijmegen, The Netherlands and President of the European Society of Pathology, adds that pathologists need to learn digital pathology by building expertise. He speaks of an experience that occurred when trying to validate a particular procedure. “There was one specific case which I missed, actually twice, in the digital scan of a signet–ring carcinoma of the large bowel. I didn’t miss it in the glass slides. Interestingly, my colleague, who had also no or little experience with digital pathology, experienced the same thing. Whereas two very experienced colleagues found this small lesion and interestingly also my trainees, who take way more time when they look at the slide, also did not miss it. This example tells us me that for routine pathology, probably you can use digital pathology as well, but you have to go through a learning phase.”
4. Standardization

Liron Pantanowitz thinks that one of the significant obstacles slowing the adoption of digital pathology is standardization of the whole imaging process from image acquisition through image viewing. The industry is at a crossroads where vendors are producing different instruments and different software and different file formats. Liron says “we haven’t reached the point where the vendors and information systems are all compatible and these are plug and play systems that are easy for laboratories to adopt. I think when we reach that interoperability where everyone is compliant, where digital pathology will be really leveraged and fully available for pathologists and actually then benefit their patients.” Promoting standardization, with the participation of vendors and improved interoperability we will go a long way towards the more widespread adoption of digital pathology.

Olga Colgan, Director Commercial Marketing, Aperio ePathology, Leica Biosystems, recognized that standardization in digital pathology is a very valid and very hot topic right now. But she counselled that “We also have to take the garbage in – garbage out approach to digital pathology [and remember that] reviewing the slide is that last step in the anatomical pathology process. Really when we talk about standardization, we need to look at the preceding steps in that full process if we want to have true standardization. That goes right the way through tissue preparation, your tissue staining, your section thickness when you’re using microtomes, and all of these impact on the overall finished slide and then that’s the input into your scanner. That leads to your digital pathology.”

For Marcial Garcia Rojo, Head of Pathology Department, Hospital de Jerez de la Frontera, Cádiz, Spain, digital pathology standardization is “very, very important.” He sees that pathology procedures are changing a lot particularly by becoming more and more automated. In order for all these automations to happen fluently and to be able to interconnect different pathology departments, Marcial argues that “the only possibility is using standards”, standards that are in fact already available. Marcial says that “IT or medical informatics standards were created about three or five years ago, so they are already available and we should take advantage of them.”

Marcial sees the future as a global network of interconnected medical professional scientists. For this version to work standards are needed to:

- define the best workflow, the best turnaround times to save time, to improve the quality of diagnosis
- technological standardization that can manage file formats for the scanners, for the digital slide scanners, and deliver efficient interoperability between the LIS, (laboratory information system), the PACS, (picture archive and communications system) and the viewer

He points to three standards: DICOM for imaging; HL7 for exchanging data; and SNOMED CT to enable “semantic interoperability that my diagnosis in Spanish should mean the same as a diagnosis in English.”

Standardization does not mean that every single scanner vendor has to use the same file format: rather standards will enable them to connect and integrate their images in a global network where all pathologists can see the images and communicate these images in a standard platform.
Yukako Yagi, Director of Pathology Imaging and Communication Technology Center, Massachusetts General Hospital and Harvard Medical School, USA, has been conducting research which has resulted in changing the classification of lung adenocarcinoma. For her standardization to deliver consistency of colour imaging is key. The colour possibility is affected by many things such as staining and sample thickness and the differences between scanners producing different colours. Her work with other institutions and the industry has been on resolving this issue.

Yukako also reveals how the sheer volume of data created by digital pathology by whole slide imaging possesses its own challenges “Several years ago, we couldn’t easily image a whole slide, but because of the improvement of whole-slide imaging with scanners, we’re developing our own image analysis 3D image reconstruction software to encourage the industry. The main challenge with 3D imaging is the file size and because one image of the whole slide is about 10 GB, we are using 100 glass slides so the file size is close to 1 TB.”

“I.T. OR MEDICAL INFORMATICS STANDARDS WERE CREATED ABOUT THREE OR FIVE YEARS AGO, SO THEY ARE ALREADY AVAILABLE AND WE SHOULD TAKE ADVANTAGE OF THEM.”

MARCIAL GARCIA ROJO, HEAD OF PATHOLOGY, HOSPITAL DE JEREZ DE LA FRONTERA, CÁDIZ, SPAIN
Case Study

Paul van Diest, Head of Department, Professor in Pathology, University Medical Center Utrecht, Netherlands

What was your experience of going digital?
It has been an interesting experience for this hospital to turn digital – if not completely but at least to a large extent. It’s been a long process where many things have to happen like getting in all the IT or getting the people motivated, making all the connections between the different building blocks of the system, and then trying to actually use the system. It has been a fairly painful process, but all the people are quite enthusiastic about it and, in the end, we banged it down and I think it works relatively well now.

Many labs have been scanning slides occasionally for different purposes but when you turn to real primary digital diagnostic pathology, then this is a fairly complicated process where you may have to build a very good infrastructure but once you get it done, it has a lot of potential advantages actually.

Let me mention a few. First of all, it’s much easier to consult your colleagues digitally. It’s not like you have to run around with the slides and find someone. You can just put up the images on the server with a message, “Could you please look at this image?” At the same time, they don’t have to do it on the spot when you come through that door, but they can do it at their leisure. This is a big advantage.

It’s also that all the multidisciplinary meetings can be done digitally and also the preparation of the multidisciplinary meetings is much easier because normally all the slides are circulating. They’re on desks of residents or pathologists or they’re just being put in the archives and that means that many people are looking for slides all through the day and that really takes a lot of time, which I estimated at about one FTE on average is busy looking for slides in the lab. That’s a lot of work.

There’s a few other advantages as well. None of the slides would be missing, so you would have them available really all the time. Sometimes slides get delivered to the wrong person or I’ll ask my colleague, “Could you cover my business for today?” I forgot to tell it at the lab, and then the slides will be in the wrong spot. That’s another advantage, too.

A very important advantage could also be that the application of image analysis algorithms could be implemented into the workflow. That means you can scan the slides immediately when they are produced in the lab, and then the image analysis algorithms can run in the background and that means that the workflow becomes much better because normally when you say this is the slide where I want some image analysis algorithm to work on, you have to initiate the process and that takes time. Well, pathology is a quick business these days, so we cannot afford that. This can be done in the background when you do really primary scanning. These are just a few of the advantages that I could mention.

Can the current technology deliver all these benefits?
To a large extent, current technology is up to delivering an infrastructure that works for primary digital diagnostics but not completely I must confess. There are a lot of good building blocks available from different vendors, but still it’s a challenge to put them together. It’s not like one vendor has the complete solution that you can just carry into the lab, turn on the power, and it works. It’s not like that. That has to do with connections that have to be made between scanners, and storages, and lab information systems and speech recognition systems, and test ordering systems, and all these kinds of things. That’s one very important factor that connectivity is still an issue. It can be solved, but it’s still fairly complicated.

One other thing is that to work with the digital images in what we call a viewer, which is a program where you handle the images and scroll through it, magnify the images, zoom in, zoom out things like that, that is still a matter of concern. This is usually being done with just the regular computer mouse and the ergonomics of that are quite poor I think. This is clearly an area that needs to be addressed because otherwise people doing this primary diagnostics, working on images all the time, having to do this with a mouse will get RSI–like complaints I am quite sure about that.

Interviewed at the Digital Pathology Congress, London. 4th & 5th December 2015.

His presentation was on Primary Diagnostics in Pathology Using Whole Slide Images

“Working with whole slide images potentially offers many advantages for the pathologist. Many of these have already found their way to daily practice, like digital teaching, digital archiving, digital slide panels, and digital consultation and revision. One area which is emerging now is primary diagnostics using whole slide images. In this presentation, the ins and outs of primary digital pathology diagnostics will be discussed based on an analysis of currently available technology and literature on reliability of primary digital diagnostics”
One other issue that cannot be ignored is the fact that the US FDA has restricted the use of digital pathology for making primary diagnosis.

The Food and Drug Administration has the oversight of medical diagnostic testing as well as drugs and food. Historically, their regulation of the diagnostics industry has been relatively light. The reason why a microscope for example is exempt from FDA studies prior to releasing a new form of microscope on to the market is that it has been determined that they are substantially equivalent to microscopes that pre–existed in the marketplace prior to that act.

Whole–slide imagers have been deemed by the FDA to be different. Yes, they capture an image and yes, that image is very similar in appearance to a microscope. However, the data that comprises that image is stored on servers and it is run through electronic means that are actually quite different from a photon passing through objectives. For this reason, the FDA has declared that whole–slide imagers are class III devices. Consequently, one must first demonstrate through a premarket approval process that a whole–slide scanner is safe and effective in a patient population and those PMA or premarket approval applications have not been filed yet to the satisfaction of FDA.

As a result, in the USA, the use of digital pathology had, in general, been restricted but it’s also created different kinds of uses for digital pathology such as secondary consultation, education, proficiency testing.

In Europe, it’s a little different, without an FDA there is no formal need for any approval before actually applying the technology in clinical practice. However, vendors would like to have a CE–IVD mark – a quality mark for machines. So some of the scanners and some of the software, and some of the images algorithms now have such an approval. For Paul van Diest, that’s a good thing “because that shows us that at least the application of this technology is safe and reproducible.”

In the USA, the FDA has already cleared a number of algorithms for therapeutic diagnostic testing such as in breast markers for ER, PR, and HER2, and the question that now has come back is – is it safe to use for primary H&E diagnosis? That’s what’s being discussed and debated now. Keith Kaplan says “Fortunately, we have a growing body of literature and experience to support that in fact it is safe for clinical use and more and more discussion occurring around its use for primary diagnosis.” Keith continued that he had “witnessed is a change in the FDA. There is a more positive movement towards ultimately helping vendors in facilitating them to perform the trials necessary so that they can render claims so that digital pathology in the USA can soon be used for primary diagnosis.”

Paul van Diest adds “Some of the companies are actually working on this, so there is now consensus over a study that should be completed, and if the results are positive, then the FDA would approve diagnostic digital pathology as a diagnostic technique. Maybe in about one year’s time, that could in place.” Stephen Schmechel thinks that “once the first PMA comes through, we will see the American market open up for whole slide imaging”.
The Digital Pathology Congress is organised by Global Engage. In 2015 the meetings will be held in:

San Diego, United States, June 22-23
www.globalengage.co.uk/digitalpathology.html

Kuala Lumpur, Malaysia, September 21-22
www.globalengage.co.uk/digital-pathology-asia.html

London, United Kingdom, December 3-4
www.globalengage.co.uk/digital-pathology.html

In 2014 nearly 300 people attended the inaugural meeting in London.

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Feedback:

“I’m happy to be at the Digital Pathology Congress in London, and I feel that the current agenda addresses all aspects of digital pathology technique, past issues, current issues, and addressing future trends. I think it’s a wonderful set of speakers and a great audience really engaged in the field and helping promote the future of digital “pathology.”

LIRON PANTANOWITZ

“This conference has covered a broad spectrum of interest from the scanning through the image analysis through application within post research on the clinical field and also with the pattern recognition tissue samples come through and classification we’re utilized. .... There’s been a lot of discussions around standardization associated with digital pathology. It’s certainly given us some food for thought. I think there’s going to be a lot of collaborations coming out of this meeting, which will obviously bode well for the future of digital pathology.”

ALISON BIGLEY

“This has been a very good meeting. There is a high calibre of science and new platforms and techniques that people in the industry are performing. There is a nice mix of academic and industrial speakers”

STEPHEN SCHMECHEL

“I found the scientific content of this meeting to be extremely high. I certainly appreciate the strong level of industry support for this meeting and the level of discussion and dialogue that’s taken place at this meeting, one of the best of the year certainly. “

KEITH KAPLAN

www.globalengage.co.uk/events