whitepaper

How to Go Digital in Pathology

LABPON
Laboratorium Pathologie Oost-Nederland

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Prologue
“How to Go Digital in Pathology”

Foreword by Alexi Baidoshvili MD, Pathologist at LabPON, the Netherlands, and Project Manager of the Digital Pathology Project

The microscope was invented and developed by the Dutchmen Sacharias Janssen and Antoni van Leeuwenhoek around the 17th century. They made their discoveries with a microscope that initially had two pieces of ground glass and later only one piece of cut glass. A single lens, after all, was much less affected by distortion and chromatic aberration than a compound microscope. This invention initiated centuries of light microscopic studies of tissues in health and disease and is still very relevant for today’s health care. Microscopy is an irreplaceable tool for the pathologist in order to study the architecture of tissues and cells during diagnostics.

The microscope has a longer history with more phases than digital diagnostics. Its digitization is only one aspect of the field of pathology since this field revolves around more than the microscope. For example, the digitization and implementation of whole slide image (WSI) have been going on for years. This effort initiated by academic centers where they investigated its use for research and education and later for multidisciplinary meetings. Digitization will unlock new possibilities for both pathologists and researchers alike, with the use of image recognition and smart software that will help them to work more efficiently, increase accuracy and provides new insights. By embracing technology, the world of digital microscopy can become what the galaxy is for an astronaut. I believe that we are witnessing a turning point and that the time has come to fully integrate digital diagnostics.

At LabPON, we started using WSI in 2010 and discovered right away that we needed to have a fully digital diagnostics workflow to take advantage of all the benefits. As the first laboratory worldwide that succeeded in digitizing the entire workflow, we realize that there are still challenges ahead of us. This huge innovation is not only beneficial for our institute, but for the whole field. To make the most of our experience, we want to share our insights with every department of pathology worldwide. In the Netherlands, I experience an open atmosphere and a willingness to collaborate, which I find to be one of the most important reasons why pathology here is in the vanguard in our field. I am proud to be part of this innovation together with my colleagues.

Alexi Baidoshvili

1 Introduction

Digital microscopy (pathology) is gaining interest worldwide. For instance, in Scandinavia [1] [2], and in Canada - through the Canadian Association of Pathologists - there are now established guidelines for telepathology service for anatomic pathology [3]. Some Dutch pathology laboratories in the Netherlands are leaders in the transition to work digitally. Laboratory for Pathology East Netherlands (LabPON) is one of the first in the world to make the step to implement a fully digitized histopathological clinical diagnostics workflow.

In this paper, we provide insight into the transition to a fully digitized histopathological clinical workflow in a pathology laboratory. We believe our experience can help other laboratories complete this process smoothly and as cost-effectively as possible.

We describe our transition in the following terms: business vision, logistics, technical aspects, and ergonomics. The implementation in our laboratory was handled gradually and effectively.

About LabPON

LabPON is one of the largest pathology laboratories in The Netherlands and in Europe. It is an independent laboratory with 115 employees of whom 18 are pathologists, handling more than 55,000 histological requests per year, with a turnaround time of 3 to 5 working days. The mission statement of LabPON is to provide fast, efficient pathology service of the highest quality to physicians and hospitals. We realize this is thanks to our clear corporate vision that allows creativity to bloom without interfering with company operations.

2 The Formulation of the Business Case

General recommendation
At the time of writing, LabPON is working on a detailed flow analysis that can be used for the formulation of a business case (BC). We experienced that it is difficult to compile a basic framework for the BC, but we are convinced that the real advantages only become apparent when the organization has a clear business strategy. Therefore, we believe the most essential part of the business case is gained when a laboratory has a sharp and clear vision in mind: why do we do this and what do we want to achieve.

A preview of a business case

We have made a roadmap (for details see chapter 3), which can be used to calculate your costs. The following list is a preview of its contents, showing that "time and quality" is one of the most important gains:

1. Ceasing internal and external distribution of physical slides (Details in Chapter 7 "Working from a distance," page 14)

2. Optimization of time in preparation and execution of multidisciplinary discussions (Details in Chapter 3 "Implementation and Workflow management," page 7)

3. Digital consultation and revisions (internally and externally) to reduce the change of case mix-ups or loss of slides and reduce the time needed from several days to a few hours (Details in Chapter 7 "Working from a distance," page 14)

4. Multiple applications of digital diagnostics and pathology case viewer. Some examples that are already used in daily practice (Details in Chapter 4 "IT," page 9).
   4.1. Total overview of the daily diagnostics, including the size and status of case studies, a simple sorting function and an instant view of the tissue section
   4.2. Measurements and counting on the section (Details in Chapter 8 "New developments," page 16).
   4.3. Parallel viewing when sections can be digitally placed side by side, or superimposed on each other

5. Image analysis is under development, and we expect that these enhancements to help us diagnose more efficiently, more quickly and qualitatively better (Details in chapter 8, New developments, page 16).

Shortlist: "How LabPON went digital according to management"

Henk van der Veen, CEO of LabPON, about the cost-effectiveness of working fully digitally

"The revenue model is not based exclusively on acquiring scanners. It is an investment in an entirely different workflow. It is far more profitable to have our diagnostics fully digitally, because the whole process will be transparent, and it streamlines the infrastructure. The real revenue lies in the increase in efficiency. It will make pathology better compatible with external and consultancy services. This larger scale will result in a much better quality, and it will be a vital link for the sub-specializations within pathology as well. It will transform the market."

Cost-effectiveness in practice

A pathologist at LabPON about the optimization resulting from digital pathology: "Digital diagnostics forces the organization to critically examine, for instance, whether to use special or routine

staining, and to take a closer look at the efficient processing of sections. Take, as an example, the number of lymph nodes that need to be removed in a bowel resection. When there has been a lot of unnecessary cutting done by the laboratory assistant, the pathologist will need to spend more time in microscopy, use unnecessary resources and perform redundant actions. Partly due to the desire to reduce storage capacity, we have critically examined the required number of sections per slide. For most cases, one or two sections per slide will be sufficient. This is just one example of what the critical examination of your process can mean to your organization and how this pushes you towards standardization in every aspect of the workflow."

Digital analysis of the current software system

Van der Veen: "We are pioneers of the movement towards a fully digital workflow in pathology, which we believe to be irreversible. Early on, we recognized that it was not going to be just about buying a scanner. I noticed that Philips is a company that has always been willing to invest in the development of software. We started with a digital analysis of our current software system. This provided insights that formed a powerful basis for our revenue model. This was necessary because the whole infrastructure will need to be revised, and it will be difficult to justify the investments necessary for this transition. It is not simply a matter of replacing existing equipment; it requires a total new workflow. To complete this transition, you will need to have an understanding of strategic matters as well as confidence." Van der Veen has interwoven this progressive view with his business philosophy, propelling pathology forward with entrepreneurial spirit.

Prevention of claims

Digitizing the diagnostic process will greatly reduce the chances of "mix-ups" with patient data caused by material or data handling. At LabPON we integrated a pathology case viewer, IMS and LIMS. It prevents errors that can occur when for instance the tissue image of one patient is assessed in the case viewer and incorrectly reported to another patient in the LIMS. Studies in the US show that pathologists are likely to receive claims [4] and that specimen "mix-ups" are the number one cause of system errors. [5] Furthermore, they have little faith in their in-house system to deal with such errors adequately. [6] Given the high overhead costs related to these claims, the benefits from decreasing handling errors should also be considered for the business case. LabPON advises laboratories that have no experience in this matter to keep in mind that one claim can lead to a significant increase in their liability insurance premium. Considering that almost all pathologists have been involved with errors in various steps of the diagnostic process, [6] full digitization of the diagnostic process will likely lead to a major reduction of the risks of system errors.

We recommend thinking carefully about the transitional path and what your applications will be. By doing this, you will ensure that the transitional process will take up the shortest time possible and it will cost you less as well.

An overview of the different applications

1. **Full digitization of the workflow:** LabPON has clearly defined their applications in advance: consultation, specialization, education, intraoperative consultation, and the ultimate objective of the transition to fully digital diagnostics for histology. Because LabPON has aimed to work fully digitally, they will reach their return on investment sooner.
2. **Consultation:** Digitization enables that subspecialties can develop faster on four levels: internal, regional, national, and international.
3. **The integration of diagnostics into the cancer treatment chain:** This strengthens the position of the pathologist since diagnostic information is accessible to other areas. As a result, the pathologist can closely collaborate with, among others, the radiologist, microbiologist, clinical chemist, and medical geneticist. Big data can be shared very easily in this manner.
4. **Image recognition systems:** Full implementation of the digital workflow in pathology allows image recognition to link data, with the aim to improve the workflow, and ultimately will help to improve the diagnostic process, by making it more efficient, faster, and of a better quality.

3 Implementation and Workflow

Using a project-based approach, LabPON started the implementation of digital pathology in 2010. Though this was a labor-intensive process, the management team has kept all collaborating parties engaged. Leadership and well-organized change management have been the driving force behind the success of this project. We advise other laboratories to make a workflow analysis at the beginning of the transition and after implementation, because then you can visualize the real workflow optimization. To measure is to know.

Roadmap "How to start"
Below you can find a list of recommended steps when implementing a digital workflow. Taking these steps in this order can determine the success of your implementation. It is very important that all necessary IT adjustments have been tested and improved before purchasing a scanner. When the scanner has been bought, it is important to screen and optimize the software of the pathology case viewer. To prevent repetitive strain injury (RSI) and improve the user-friendliness and interface, we advise to address these issues from the start of the process. Monitors should be set up for the individual user. Ensuring the internal basis for the user is rock solid before setting up the external lines will greatly benefit the infrastructure.

Roadmap how to start
1. Make a workflow analysis of your laboratory
2. Develop a good business plan and an action plan
3. Optimize the IT system (internal and external network, bandwidth, switches)
4. Purchase scanner (technical, image quality, interfaces with LIMS)
5. Screen and improve pathology case viewer
6. Set up interfaces (touchpad, trackball, short key)
7. Set up monitors
8. Install distribution software
9. Set up external network including consultation and revision
10. Set up remote work
11. Set up frozen section diagnostics
12. Develop and use image analysis software

Workflow analyses leads to a faster workflow

A recent study shows that digital pathology may delay the diagnostic process. [7] LabPON sees digitization as an addition to microscopy. In 2013, we investigated the way in which digital diagnostics can actually lead to a faster workflow and higher turnaround time using flow analysis. Our analysis shows that experienced pathologists diagnose just as quickly with both methods, and that inexperienced pathologists are analogously slightly faster. We only examined the diagnostics time and disregarded the logistics of the workflow. Other studies show the same results: the duration of a digital diagnosis is very similar to that obtained by traditional microscopy. [8] Therefore, when we take the whole logistical process into account, digital diagnostics is faster. Another investigation at LabPON shows that working with multidisciplinary team meetings (MDT) in digital diagnostics instead of with physical slides, results in saving 28 hours of administrative work. This is a gain of about 0.7 FTE administrative position.

Since we can compare the workflow from 2013 with the current workflow, the increase is measurable and further improving. This improvement is partly due to optimization of pathology case viewer tools. The accessibility of the files include also a great improvement of the workflow. Functionalities such as measurements, counts and parallel viewing support this.

The technical workflow versus the virtual one
Digitizing the diagnostics workflow begins with a clear concept of how this should be undertaken. This can only be done if the workflow has been defined from receipt of material to the final report.

Traditionally at LabPON, there was a peak in the amount of physical sections for the pathologist in the morning, followed by quieter periods in the afternoon. Although nothing has changed for the cutting of the sections, this is no longer the case in the new workflow. Technical and logistical improvements in LabPON have enabled a more steady, continuous flow with fewer peaks. To adapt our faster and more efficient technical workflow even further, LabPON has purchased processors that are able to process tissue during the day.

Digital slides are routed continuously to the pathologists, according to the distribution of the WSI. They see straightaway the new additions to their daily worklist and decide to handle it immediately or to do it later. Pathologists are able organize their time more efficiently. In addition, they no longer need to work in the laboratory, as the diagnostics can be performed anywhere, including from home. Working from home allows them to only concentrate on diagnosis and enables them to work faster, more flexible and more efficiently. [9] [10]

Every day, two specially trained technicians and a maximum of three pathologists in LabPON do the grossing. LabPON has the ambition to train these specialized technicians to gross all the sections under supervision. Nowadays, the pathologists dissect most of the larger oncological specimen themselves, which is common practice in most pathology laboratories in The Netherlands.

Nostalgia and a new world
In 2012, in addition to working with the conventional microscope, the pathologists at LabPON were given the option of working digitally with the aim of eventually going fully digital. Studies have shown that the attitude of the pathologist towards the digital workflow is important. [11] [12] The duration of the transition varied from three to eight months, depending on the pathologist. The most difficult part was to learn to trust the digital image. Letting go of the traditional way is not only a technical experience, but also a nostalgic one. Since the microscope is a symbol of the pathologist, they might have found it difficult to let go. Though the old way was good, the new way has no principal boundaries. Over time, the number of new applications will increase and it will become clear what this innovation will mean to the profession. Wistful feelings will give way to enthusiasm for this way of working, since its benefits clearly outweighs those of the conventional way of working. A new world is on the rise.

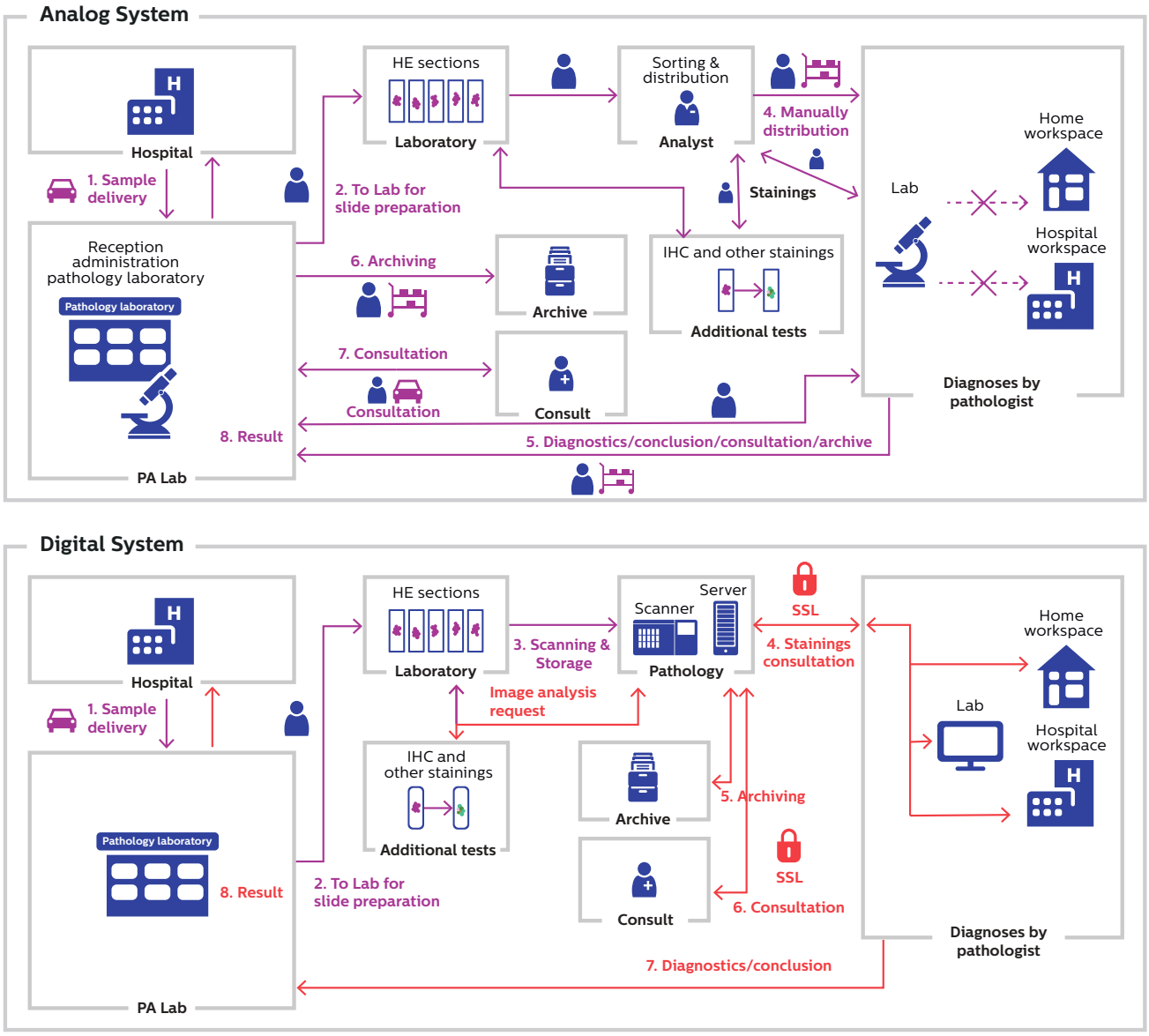
Why not to push the staff to go fully digital

At LabPON the management set a date when all pathologists would ideally work fully digitally. LabPON recommend that other laboratories make the transition gradually and as smoothly as possible, without the pressure that a deadline may cause. The big difference for LabPON was that - as a pioneer - our process is evolutionary. We tried to work with a deadline, but it did not work for the best. Therefore, we do not advise this. Instead, laboratories should pay attention to having a good training program and review all your digital applications.

We also advise shortening the time of the transition as much as possible by offering a good training program. The shortest possible transitional time also reduces expenses.

Summarized:

1. Approach pathologists who are enthusiastic early adopters
2. Involve and coach them in drawing up a training program
3. Make sure they all receive proper training in digital applications to maximize the benefits and improve the efficiency of their work
4. Implement the process organically and organize recurring digital viewing sessions with the participants



Pathology workflow for histology cases

4 IT

Philips has used its experiences with comparable projects in radiology for the IT development in pathology. Together with LabPON, they worked out the digitization and implementation. The developers learned a lot from their dedication to this project, and it improved their ability to solve problems. Essential to this new system was the software development and implementation. Helped by their move to a new building in 2012, LabPON had the unique opportunity to critically asses the structure of their software system. Nowadays, LabPON offers WSI via a server without delays or interruptions, and stores many GBs of data simultaneously. Pathologists are able to retrieve WSI from this server easily.
The standard digital connections are essential to the safety and efficiency of the pathology case viewer, image management system (IMS) and the Laboratory Information Management System (LIMS). Based on experiences, these connections were adjusted and improved each month.

The on-screen worklist offers a very good overview for his diagnostic work.

Pathologist case viewer
The case viewer offers new possibilities, allowing the pathologists to see at a glance the diagnostic cases scheduled for that day. They can see the daily list of tissue numbers, section numbers and medical service requests, and sort this list by preference. The software keeps track of what the pathologist has seen per case study and per section.

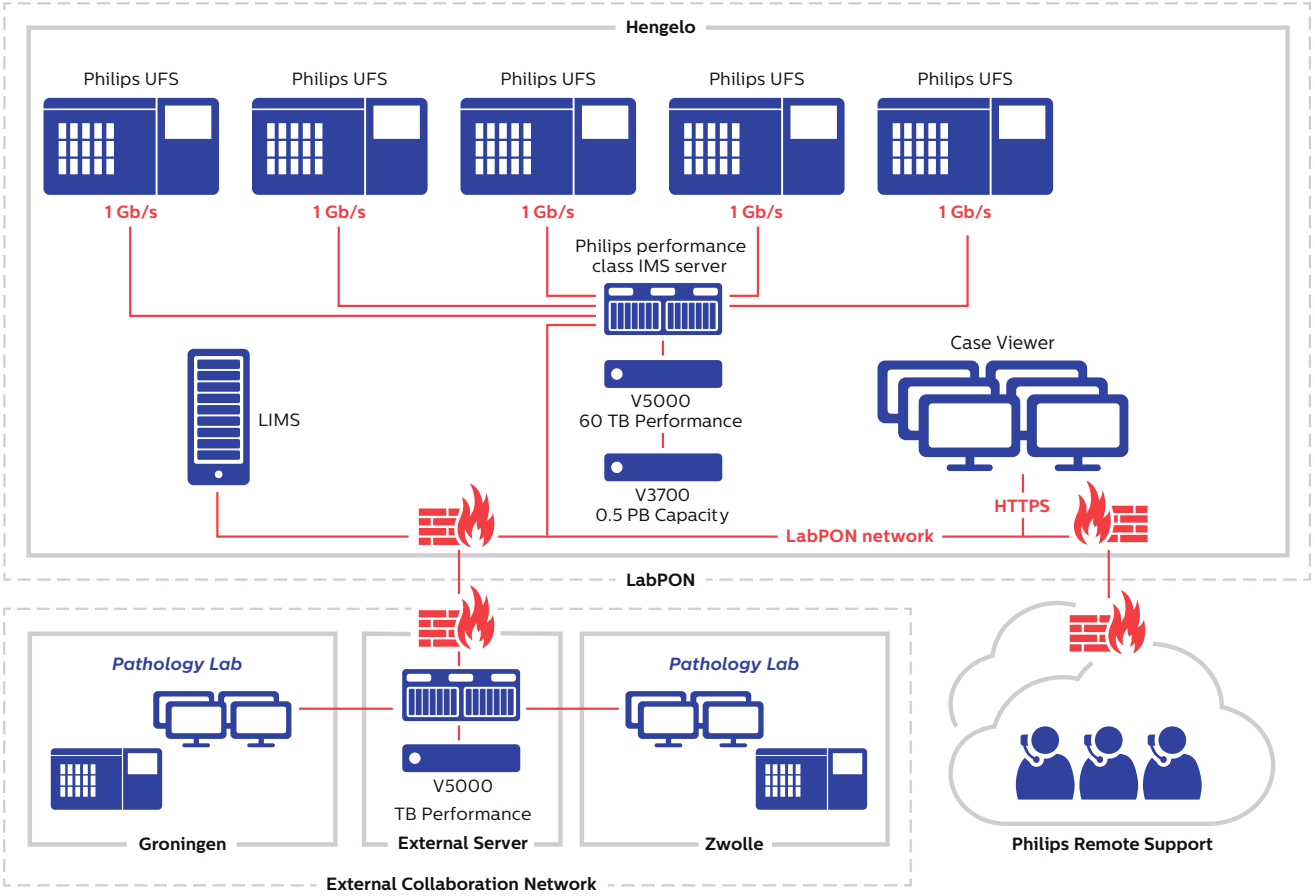
Case viewer and the connection with a Laboratory Information Management System (LIMS)
Dr. Nina Kooij, Pathologist at LabPON: "A full, bidirectional communication between pathology case viewer and LIMS is necessary to complete the digital diagnosis process. Viewing digital slides, reporting a case in the LIMS, and requesting additional stains need to be part of a logical and fully linked system that has to be acceptable for the pathologist reading the case. It also has to prevent case mix-ups.

To make sure that we can efficiently and safely read and sign out a case, we are in the process of developing a fully connected system that synchronizes in both systems important aspects, like changing the case viewed and assigning a responsible pathologist, resident or technician.

Scanning of the slides is executed directly after the staining and drying process steps. The case can be assigned to a case holder/ pathologist in either case viewer or LIMS, depending on the preference of the laboratory. This will also change the case holder in the linked system. In the future, we hope to have developed a routine for assigning cases automatically, making it possible to assign cases while they are being scanned.

The case is placed in the folder 'In preparation' as soon as the first slide is scanned. The total number of expected slides will be sent by the LIMS in response to the request for information after the first slide is scanned. This requires an option in the LIMS to indicate whether a staining is suited for scanning, and to set an accurate number for the expected amount of slides. As soon as all slides are scanned, the case is moved to the folder 'For review' and ready for the pathologist to read and report.

Requesting an additional stain should move the case to an additional folder in both systems to indicate that the case is once again incomplete. When the additional stains are scanned, the case will be returned to 'For review'.
Signing out will move the case to 'Finished' and will prevent any



changes by the pathologist who signed the case in both systems, unless the case will be reopened by an authorized person. Changing a case in either pathology case viewer or LIMS will cause the other system to follow, if the case is available, or to go to a blank screen if there is no matching case found. A speech recognition system will advise the user to save or delete the case, or to finish the current case.
It is essential to have both systems fully linked. This will prevent mix-ups, but it will also make the system more convenient for the pathologist."

Influence of the computer processor on the speed of image rendering during the whole slide imaging

Introduction

Several elements play an important part in the diagnostics workflow of digital pathology in order to ensure the working convenience and speed of work. One of them is the speed of image rendering within the viewer. Faster image rendering results in a quicker diagnosis. For rapid image rendering proper equipment such as a good computer and a fast network are indispensable. In this study LabPON investigated the influence of the computer processor on the speed of image rendering. We measured the time of image rendering on three computers with different processors with a noticeable difference in performance. Measurements were made on computers with and without a pathology case viewer-LIMS connection. The connection of case viewer with LIMS is very important in the digital workflow because it ensures that digital diagnostics is safer than diagnostics with a microscope, since it can avoid handling errors: a good connection displays the correct image for each patient.

Method

We ran our tests on three computers: computer 1 had a Core2Duo E8400 with 2 cores and a speed of 3.0 GHz; computer 2 had a Core i5-650 with 2 cores and a speed of 3.2 GHz; and computer 3 a Precision T1700 SFF XQC E3-1241 V3 processor with 4 cores and a speed of 3.5 GHz (table 1). Measurements were made on areas in the WSI that the computer had not yet put into focus. This is an accurate way of measuring because they had to be downloaded from the server and were not preloaded. Hereby measurements at these areas are comparable. During this process, the region of interest was moved continuously to a new area. The time to focus an image in the WSI was measured using the onscreen receding timeline from Windows 7. Time was measured in seconds and in the same way for each measurement.

Results

As can be seen in Graph 1, image rendering was faster on the test computers that had no case viewer-LIMS connection. According to the average time length, image rendering with case viewer-LIMS connection was almost twice as slow. Overall, the computers with faster processors outperformed the slower ones. On the computer without case viewer-LIMS connection but with a normal user interface of a special connecting tool and a "space navigator" with a connecting tool, image rendering was slower but only slightly so.

Discussion

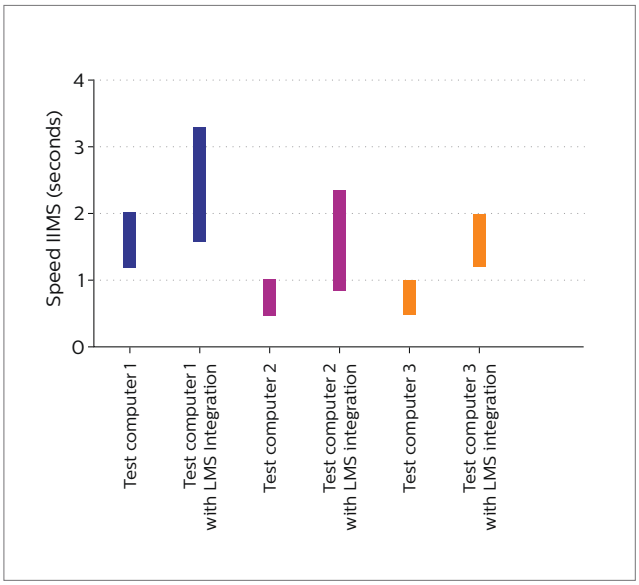
Our results show that the speed of the computer processor influences the speed of image rendering in case viewer. To prevent speed reduction after connecting the IMS with LIMS, this connection should be well prepared and all processes should be checked in advance. Other computer specifications may also play a part such as a graphics card, since digital pathology requires images of high quality and a minimum of least two monitors.

Test computers

All computers were equipped with operating system Windows 7

	(test computer 1)	(test computer 2)	(test computer 3)
Processor	Core2Duo E8400 3.0 Ghz	Core i5-650 3.2 Ghz	Precision T1700 SFFXQC E3-1241 V3 3,5 Ghz
Memory	4 GB	4 GB	2 X 4 GO DDR3-1600
Hard drive	120 GB SSD	120 GB SSD	256 GB SSD
Video Card	Matrox M9128 LP	Matrox M9128 LP	NIVIDIA QUADRO K620

Table 1 - Specifications of the computers used in the test



Graph 1, Speed image rendering in seconds for 3 computers

Storage policy and Security

Policy of LabPON

LabPON is a diagnostics laboratory, which means that most of its archived images will not be used after 6 to 8 weeks. We have therefore chosen to store the digital images accordingly and to remove them after this period. The archived glass slides are stored for up to 30 years under normal guidelines.

Since the Dutch Pathology Association is discussing legal regulations for digital pathology, there is no legal framework for image storage. However, it is permitted in the Netherlands to make a diagnosis based only on digital images. [17]

Why archiving all slides will be required

Archiving WSI will make it easier and more efficient for you to prepare for multidisciplinary team meetings (MDT) because:

1. Comparisons with previous diagnoses (revisions) are easy to retrieve
2. Reviews can be viewed simultaneously. Everyone is looking at exactly the same image
3. It saves time by eliminating archiving work
4. The quality of WSI remains constant contrary to glass sections, which are fragile and can fade
5. It also covers research and education purposes

The present and the future

LabPON has a server with a capacity of 89 TB, which is enough for about 2.5 months. Storing our entire WSI would require about 450 TB per year. We believe that in an ideal world all files should be stored at two different locations. This would ask for a storage

capacity of 900 TB per year, based on the average size of a scanned tissue sections at LabPON. The necessary storage capacity depends on the scanner type and the workflow. For the latter, it is important to consider the way the sections are scanned (40x or 20x), what kind (mix) of material they have (are there many biopsies or resections?), and what kind of protocols are applied when cutting the sections; for example, are there many sections for each case and/or large tissue sample on cassette? 3-D scanning can also greatly affect the needed storage capacity. As a result, the space for the same number of cases can differ greatly per year and per laboratory.

To reduce the required storage space, Philips is developing smart storage software, which allows the WSI to be stored more compactly, while keeping the quality of the image intact. Many reliable solutions have been devised to guarantee the security of the server. The current focus is on dealing with the file size, leading to possible cost reduction in storage, while speed and quality of the server are constantly being improved.

Reasons for LabPON to delete images after 6 to 8 weeks

Image storage is one of the main bottlenecks. At this moment, LabPON cannot afford to store all their WSI permanently. We are waiting for new developments that will make storage more cost-effectively, e.g. by compressing images. This position is similar to that of other (nonacademic) pathology laboratories in The Netherlands that diagnose partly with WSI. Some academic centers, such as the University Medical Center in Utrecht, store all their WSI permanently, but they archive their glass slides at the same time. These physical slides are used for study and research.

5 Scanner

A whole slide scanner is essentially a computer-controlled microscope that is attached to a camera with advanced sensors. Some scanners have pre-focusing functionalities. The following are the general components of a scanner. [11]

1. A microscope with lens objective
2. A light source (bright field and/or fluorescent)
3. Robotics to maneuver the physical slide swiftly inside the machine without breaking the slide
4. Digital cameras to capture the WSI
5. Computer hardware
6. Software for a fast and secure digital infrastructure and management, and for visualization of the WSI
7. Option to scan fluorescence
8. Option to do automated quality control and automated rescan

Choice of scanner

There are different kinds of scanners. Before you buy one, you should decide what kind of scanner you need. They can be used for research, education, consultation, and diagnostics. There are several important components to consider, and the target is a very important one. You should look for a scanner that is easy to operate, provides good image quality, has high throughput with low re-scan rate and is affordable.

LabPON tested scanners from different venders for a longer period of time. During our tests, we noticed that there is room for improvement when it comes to 3-D scanning, image quality, sections, improving areas that are out of focus, and more.

Points to consider when purchasing a scanner:

1. Image quality (the higher the quality the more details you will see)
2. Speed of scanning
3. Size of the files (see our chapter on storage on page 11)
4. User-friendliness
5. 3-D scanning option
6. Option to scan big slides

Software	Usability	Image quality	File size	Speed	Viewer	Price
Good	Good	Moderate / Good	800 Mb to 1500 Mb	Good (+/-2.5 min)	Moderate	€ 180,000.00
Moderate	Moderate	Poor / Moderate	500 Mb to 1 Tb	Moderate (+/-3.5 min)	Moderate	€ 140,000.00

Table 2 digital pathology system evaluation

Choice for the Ultra-Fast Scanner

LabPON choose for the Philips IntelliSite pathology solution because of the high quality of its technology and its ease of use. Limitations like lack of 3-D scanning, scanning big slides and fluorescence did not play a big role.

CEO van der Veen about the price of scanners: "All scanners now available will have to be reduced in price greatly, because they are so expensive that implementing them in the workflow is less cost-effective and therefore less attractive. A serious point to consider."

The use of the scanner in the diagnostic workflow

LabPON works with four high-throughput Ultra-Fast Scanners (UFS) and one backup scanner. The technicians usually run four scanners simultaneously. Most of the daily turnover of slides are scanned at night and distributed in the morning to the available pathologists. However, because of the continuous, nonstop

workflow, the technicians also use the scanners during the day and divide the slides equally among the scanners.

- Racks are used simultaneously with a total capacity of 300 slides
- Average scanning time in LabPON is +/- 2.5 minutes per slides; +/- 50 minutes for one rack of 20 slides
- During the peak times there is more than 400 MB of data transferred from the scanners to server each second

Validation scanner

The objective of the validation was twofold: are the WSI good enough in comparison with a light microscopic image, and are the technical aspects of digital and diagnose critically assessed?

The initial validation of a scanner was done with 173 diagnostic case comprising 1042 slides. The normal composition of the day of this routine diagnostic laboratory is used as standard. In this validation LabPON has not specified the differences in scanning time in relation to the average size of the slide deliberately. These cases were digitally diagnosed by a panel of three pathologists. After three days, the panel diagnosed the exact same material through a light microscope.

At LabPON there are on average 800 slides produced per day. If 0.4% cannot be diagnosed digitally after scanning, it would mean that three slides should be re-scanned per day. We found no obvious problems in diagnosing WSI. The daily number of slides that need to be re-scanned is deemed to be acceptable (an average of three per day). We concluded that WSI with these scanners is suitable for diagnostics.

Scanner areas for improvement

Occasionally, mechanical problems could occur when grabbing or moving slides with current technology scanners. This is often related to slide related issues, such as sticky, not well dried out, or incorrectly covered slides. The scanner will give an error message and will stop processing. This is an area for improvement for both laboratories, as well as the use of less sensitive technology within the scanner. But there are more challenges to overcome in the area of slide scanning. Scanning 3-D images is still problematic. Specifically long scan times and huge data files generated are a big challenge. 3-D images are important especially in cytology diagnostics. Another improvement opportunities are with the selection of settings for scanners. The reduced sensitivity setting, to increase scanning speed, sometimes causes problems with skipping a small piece of tissue. This can have major negative implications for diagnostics. Especially, light fabrics such as adipose tissue and immunohistochemical stained slides can be difficult to scan.

6 Ergonomics

In several studies, ergonomics is named as one of the benefits of working fully digital. [2] [9] [11] The transition from analog to digital diagnosis naturally results in lesser ergonomic problems from working at a microscope, mainly neck and shoulder pain. During the transition to working fully digitally, LabPON monitored the ergonomic aspects of our workflow, and it became clear that unilateral movements with a mouse in particular pose a risk, because of their repetitive nature, resulting in repetitive strain injury (RSI). Therefore, we looked for ways to vary between interfaces. Our solution for this problem is to use more than one device. In collaboration with Philips, we developed a selection of tools for different devices.

Keyboard shortcuts

Philips made efforts to minimize the number of clicks by developing an efficient user interface which allows the use of keyboard shortcuts. This resulted in user-friendly software that is more intuitive to work with.

Touchpad

We developed a touchpad tool and a tool for the “Space Navigator” to prevent RSI symptoms. The touchpad works in the same way as a tablet or mobile phone and allows pathologists to choose their user interfaces.

Monitor

At LabPON we looked into the quality aspects of monitors to find the best one for digital diagnostics. We experimented with monitors and found that almost all monitors are good for diagnostics, although we recommend higher quality monitors.

Selecting the right monitor:

1. Use at least two monitors. One for the normal workflow and one that replaces the microscope and is used for viewing the WSI.
2. Use a monitor of 24-30 inches (61-76 cm). In our opinion, the best size is 27 inches. The screen should not be too small so you can still see all the details. The screens should also not be too big, otherwise the pathologist will risk too much head movements.
3. Use two monitors of the same size and the same models. This is important because different monitors have different letter sizes and different colours, even after calibration.

7 Working from a Distance

Digitization creates new applications and possibilities for performing diagnostics from a distance, making it even possible to perform them from outside the organization. Working from a distance is a big benefit of digital pathology. [10] [11] Here we discuss several internal and external applications of pathology from a distance, also called telepathology. Once a pathology lab workflow is fully digitally, regional and national digital networks and platforms can be set up, which can improve the diagnostics. LabPON is setting up a regional network in collaboration with the University Medical Center Groningen (UMCG) and Hospital Isala in Zwolle. Also, international consultations are digitally much simpler and better accessible. The biggest challenge of external consultations is security in transmission of patient information. With the use of digital pathology and its ability to send images (WSI) digitally for external consultations, it has become very topical to send patient information securely to other laboratories. For this several options have been identified. Recent developments will soon ensure that external consultations can be done, within a very short time, digitally.

Internal consultations

At LabPON we have an internal digital network for consultations. Thanks to technical and logistical innovations these consultations are more widely accessible. Moreover, subspecialties are easier to plan and maintain, knowing that there is a minimum number of cases a pathologist must view for their subspecialty.

Remote diagnostics

Being able to work from a distance has many advantages. For planning and organizing it provides peace of mind knowing that working space will not be an issue. There are currently no official regulations for remote diagnotics, but LabPON advises using the same technology as in the main workplace.

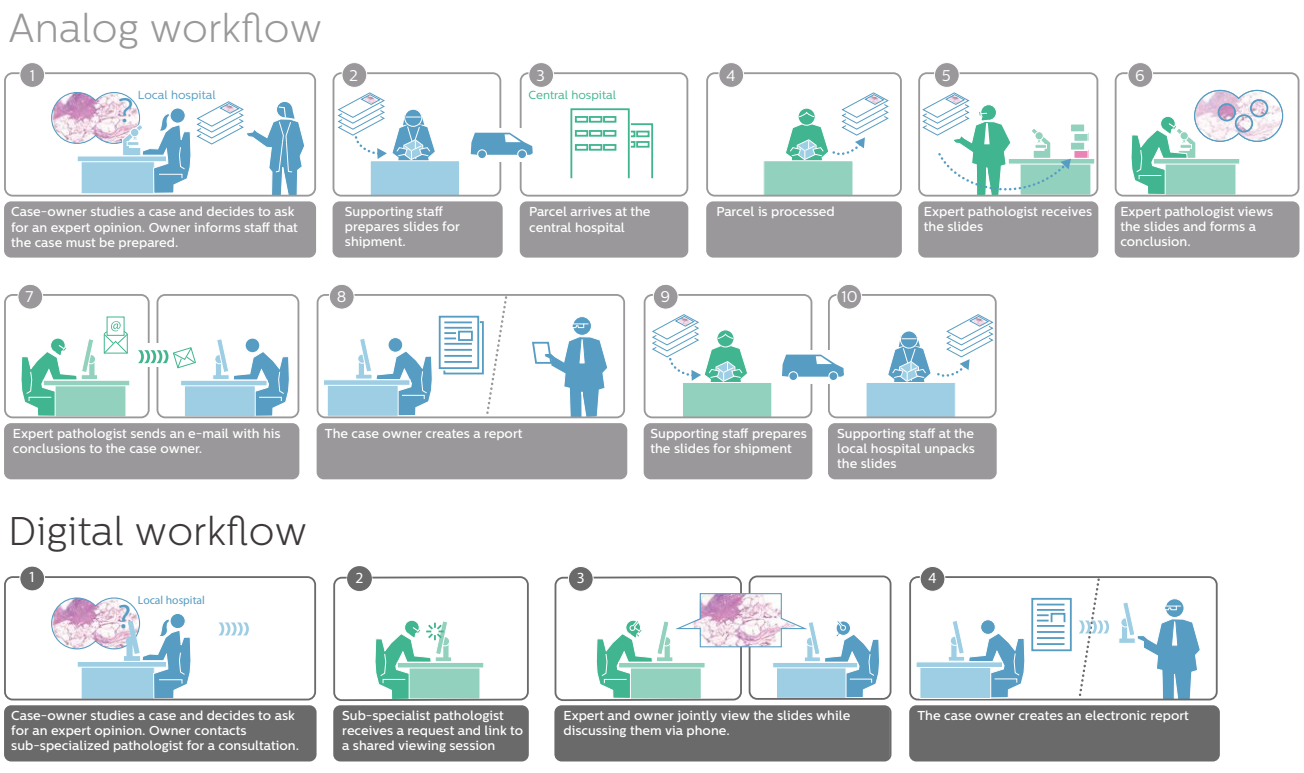
A few examples of the benefits of working externally:

1. If the pathologist cannot go to work, perhaps due to a sick child, poor weather conditions or traffic issues, he can still work from home.
2. When a pathologist has an external meeting, conference or appointment that takes up part of the working day, he can still use the remaining time to work from a distance and can be consultated for specialized cases.
3. Part-time pathologists have the possibility of completing histopathology cases outside the laboratory after office hours without having to ask a colleague for assistance.

The security of the digital connections is guaranteed by Citrix connections. For outside work we use a dedicated Virtual Private Network (VPN).

Frozen section services

LabPON provides intraoperative services for several hospitals. We want to use remote diagnostics for this as well in the future.



Consultation: analog versus digital workflow

Currently the pathologist and the technician who cut the frozen section have to travel to, in our situation, an Operating Room (OR) in another hospital. If the surgery takes longer than expected, as is often the case, the pathologist may have to wait for several hours. Digital pathology can potentially smoothen this procedure in the future. We envision that the technician could, with the on-line aid of a pathologist, perform the technical part on-site, scan the slides digitally and send the WSI to the pathologist. Then the pathologist can evaluate the case behind his/her desk and even easily consult a colleague if necessary, while working in the leisure of his/her own workplace. This digital workflow thereby guarantees a better, more cost-effective diagnosis, since traveling and waiting time could be reduced. However, this is not yet implemented in our diagnostic workflow.

External services

LabPON is a nonprofit organization and we support other laboratories when they are temporarily understaffed. Thanks to the digitization of our workflow, it is more efficient, allowing us to provide more of these services to external partners. [13]

Developing a network of pathologists

Together with the hospital Isala in Zwolle and the UMCG, we are working on a digital network that will connect their pathologists as well. We notice that our team of pathologists are consulting their colleagues in this network more frequently.

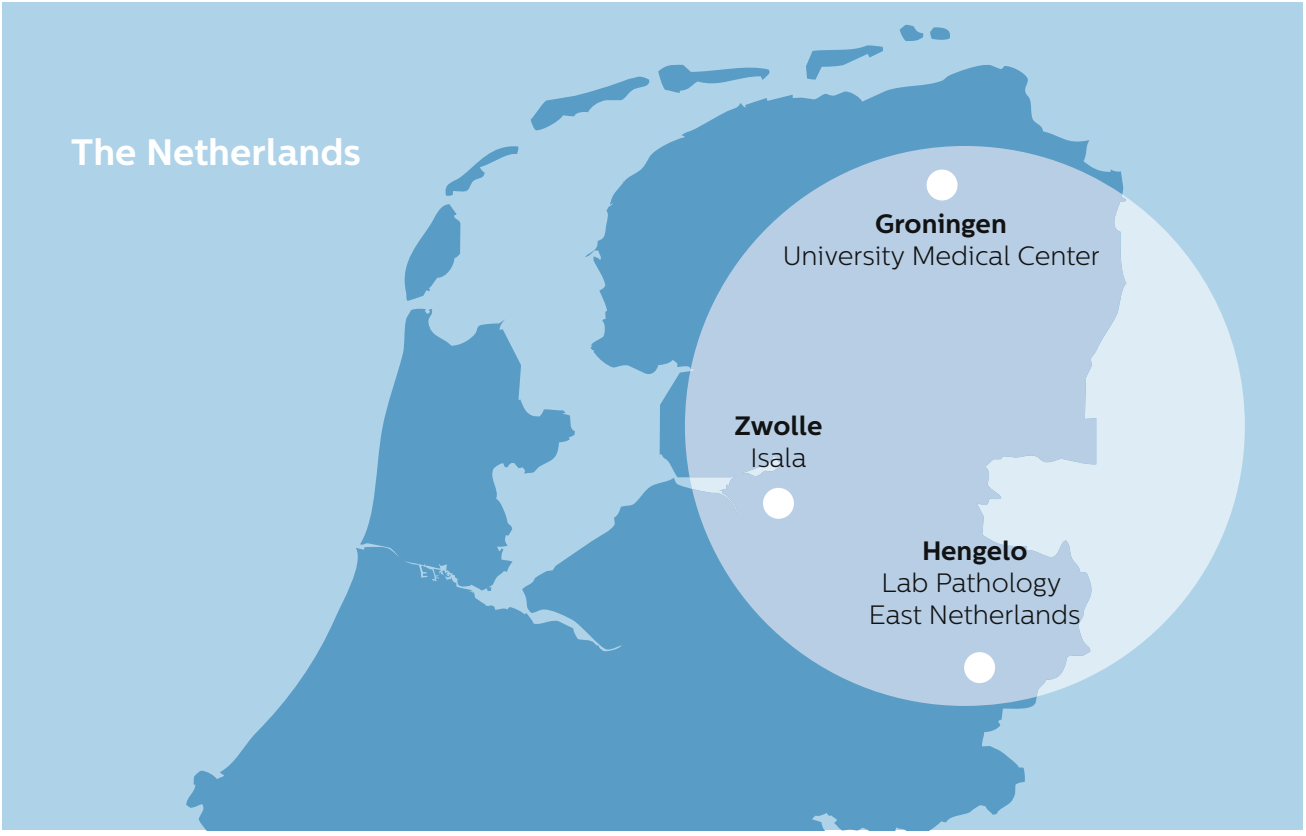
Regional digital network

Dr. Jos Bart, pathologist at the hospital Isala in Zwolle: "At the moment we are working together with LabPON and the UMCG on creating access for all of the almost 50 pathologists to patient data and corresponding microscopic images on one central server. This regional network could be expanded into larger networks, and we are starting with the three institutes. Philips has a remarkable amount of knowledge and is very skilled in the software that is part of the infrastructure of digital microscopy, much more so than other suppliers, and we benefit gladly from their expertise."

Pathology image exchange project

The Dutch Society for Pathology (NVVP) has created a working group to set up a national platform that will enable laboratories to exchange their WSI. This project, called PIE (Pathology Image Exchange), is affiliated with the PALGA Foundation. PALGA is the Dutch national database where all reports generated by all Pathology departments (academic and nonacademic) are stored, as well as a network for data exchange for all pathology laboratories in The Netherlands. Every laboratory in The Netherlands has been approached to be a part of this project. Working group member Professor Paul Van Diest of the University Medical Center Utrecht (UMCU) about the ambitions of this national initiative: "Many consortia are setting up local digital networks at this time, but it is extremely complex to connect everything. What this working group is doing, in parallel to these local initiatives, is developing a national image exchange platform for all to connect."

Professor Philip Kluin of the UMCG: "In 2008 we started projects related to external networks at the UMCG, which involved LabPON and hospital Isala in Zwolle, but also the Martini Hospital in Groningen. We turned our focus quickly to the digital connection with and the secure integration of PALGA where all patient data is managed since this is necessary for returning a regular report and claiming a consultation digitally. To avoid confusion and delay a pathology report must be linked safely and directly to the corresponding digital images. It takes times and a good collaboration of the different IT departments to implement a flawless consultation system within the region and the country. Establishing a central server that will connect LabPON, Isala and UMCG is definitely a good idea, but it is also a challenge to integrate the necessary patient data on one server. That is why I am very happy with the national initiative PIE and the way PALGA is managing and controlling the exchange of patient data. Digital pathology will improve collaboration between the centers, both regionally and nationally."



Regional digital network

8 New Developments

The techniques behind digital pathology are not new, but important steps in the IT have been made allowing for a faster progress. In this chapter, Alexi Baidoshvili illustrates current refinements and gives insights into future developments in pathology.

Faculty of Technical Medicine, Technical University of Twente

LabPON collaborates with several partners, including the faculty of Technical Medicine at the Technical University of Twente. This faculty offers strong technical training but also has a very extensive medical program. Nowadays the technical professionals think along with the medical specialists making it more likely to come up with suitable solutions.

Image analysis

Pathologists have to quantify often. Any help in this area is highly appreciated. Software can do this work more precisely and more efficiently. This sort of assistance is akin to having someone who handles the preparatory work. For example, if a pathologist marked in the LIMS the cassette that contains the tumor during cutting a section, the software can automatically grade the tumor and perform other quantitative calculations. A good image recognition program can locate and grade the tumor as well. This will save a lot of time, for example in the assessment of a prostatectomy. [14] [15] We want to collaborate with the Radboud University Medical Center in Nijmegen, the UMC Utrecht, UMC Groningen and the University of Twente to further develop this software. This is one example of an important tool that will resolve qualitative and quantitative problems and may help to improve the diagnostics.

Image recognition techniques for HE staining

Jeroen van der Laak, Research Group Leader in pathology at the Radboud University Medical Center in Nijmegen, is working with a group of eight researchers on further developing an image recognition system. The group focuses on the content of image recognition techniques for HE staining in the diagnostic process. [16] Jeroen van der Laak agrees with Alexi Baidoshvili that digitization of pathology is one cornerstone of the profession's progress. The implementation of image recognition techniques will refine the work of the pathologist.

Patient treatment plan and prognosis

Digital tumor images allow for a closer examination of the tissue properties. [17] This is one of the latest techniques whereby tissue properties that cannot be distinguished with the naked eye are digitally regrouped. The software classifies the tumor according to several characteristics. This method is called "Deep Learning". The survival rate of tumors related to its physical properties is subject of scientific research. Tumor tissue could be graded differently in the future. This could improve the grading of tumor tissue, which will result in more accurate patient treatment plans and prognosis by the oncologist.

'Slide' tracking

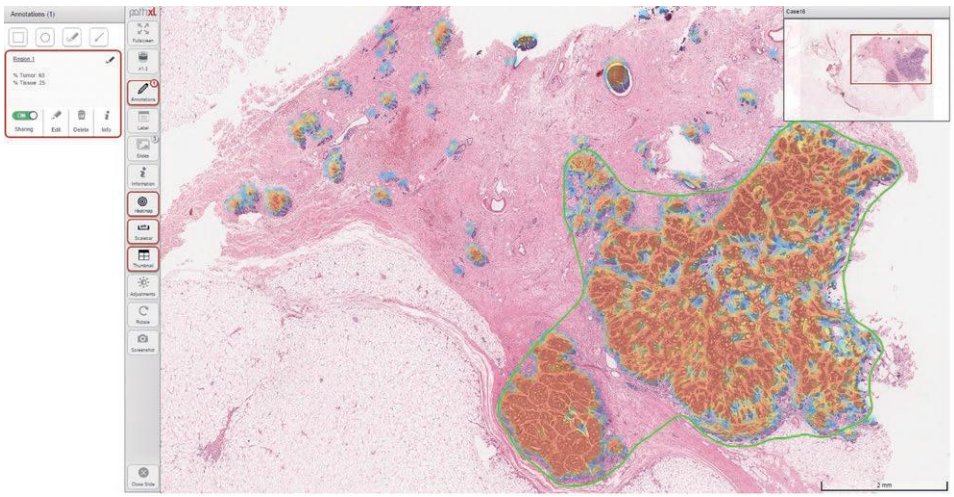
In the case of prostate diagnostics, several biopsies are usually taken from different regions of the prostate. These biopsies may be fragmented, and, as a result, part of the tissue can easily be missed under the microscope. Using WSI will prevent this because the software records and marks all areas that have not been screened. The pathologist will not only see the scanned image on the monitor but also this information. Furthermore, if a pathologist is interrupted while viewing a specimen, he will not have to start all over again when using WSI, whereas with a conventional microscopy he would still have to. Therefore, the slide tracking feature of the software toolset will save a great deal of time and prevent errors.

The "3-D scanning" for cytology and histology

A histological specimen can be scanned reliably in two dimensions, but cytological specimens and some histological specimen must be scanned in three dimensions in order to be considered sufficiently reliable. Three-dimensional scanning, however, is time consuming. Data storage requires a lot of memory. Philips is developing a technique to scan multiple layers at the same time. They also have a new technique, the "smart compression method," which reduces the necessary memory storage used. It preserves the main image on which the diagnosis is established optimally and compresses the part that was screened briefly. LabPON is going to test this further.

Molecular pathology

In the field of molecular pathology there is a method being developed that allows for malignant lesions in slides to be marked digitally for genetic research. The marked malignant lesion will be punched out automatically by a robot for making tissue arrays or molecular analysis. This development has only just begun, but it shows us what possibilities there are.



Philips Tissuemark for the automated identification of tumor tissue on standard H&E stained digital slides.
For research use only and not for use in diagnostic procedures.

> “ It is very important to formulate a good business vision”

Epilogue

The team at LabPON walked through the entire process of digitization of diagnostics. In six years we have solved many issues and invested a lot of time and money. We are now fully digital, and we are equipped with all the necessary amenities, but it is still not optimal. Because we went through this process, we gained a lot of experience and insights. Now we can better address our remaining challenges and come up with solutions. At LabPON the entire medical staff, several employees and management are committed to solving the challenges ahead and to keep improving.

Digitization of routine diagnostics in pathology is in early stages at other laboratories. Its implementation is very complex and needs to be prepared well, and requires investments. It is very important to formulate a good business vision and a roadmap based on experience instead of assumptions. To this end, we offer our insights for the benefit of other laboratories, and to serve as an example in the digitization of all routine diagnostics. This has always been one of the key drivers of our organization.

Alexi Baidoshvili

With Thanks

Alexi Baidoshvili MD, Pathologist at LabPON, the Netherlands
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Professor Philip Kluin, MD, PhD, Pathologist, University Medical Center Groningen (UMCG)
Jeroen van der Laak, PhD, Research Group Leader in pathology at the Radboud University Medical Center
Finalist - Johnny de Jong
Philips - Hans Driessen

Glossary

LabPON	Laboratorium Pathologie Oost Nederland (Laboratory for Pathology East Netherlands Foundation)
IMS	Image Management System, tracking system
Pathology case viewer	Software tool designed to get pathologists through cases as fast as possible, and having easy access to information and resources to for informed decision-making.
LIMS	Laboratory Information Management System
MDT	multidisciplinary team meeting
NVVP	The Dutch Society of Pathology
UDPS	Universal Decentralized PALGA System
UFS	Philips IntelliSite Ultra Fast Scanner
UMCG	University Medical Center Groningen
UMCU	University Medical Center Utrecht
VPN	Virtual Private Network
WSI	Whole Slide Image
PIE	Pathology Image Exchange, a Dutch initiative from the NVVP to develop a national image exchange platform
Palga	The nationwide network and registry of histopathology and cytopathology in the Netherlands

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