Digital Pathology in the Clinic: Training, Validation and Patient Safety

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The candidate confirms that the work submitted is her own, except where the work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Statement of inclusion of work from jointly authored publications

This work includes contributions from others including those working on the Leeds Teaching Hospitals NHS Trust/University of Leeds and Leica Biosystems research collaboration for digital pathology deployment. Several jointly authored publications have arisen from this collaboration and are included in this thesis.

My contribution has been as follows: I initiated and led on the projects outlined in the published papers. I designed the experiments, planned and executed the analysis, and drew conclusions from the work with the input of others where necessary.

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Abstract

Digital pathology is a technology with the potential to transform the way in which histopathological diagnoses are made and cancer diagnostic services are delivered. Despite this, clinical deployment of digital slides has lagged behind research and educational uses. This thesis describes some of the key barriers to widespread clinical adoption, which largely relate to a lack of guidance and information for pathologists regarding validation, training and patient safety. The evidence base for patient safety was analysed in a novel way to provide the basis for a validation and training protocol which was trialled in real world clinical settings, and guidance documents were developed and disseminated to the clinical pathology community to help with the transition from glass slide to digital slide reporting.

In Chapter 1, background information and an overview of the published literature regarding clinical use of digital pathology is provided. In the second chapter, the results of a national survey on access to and usage of digital pathology hardware, in addition to attitudes to digital pathology, is presented.

One significant barrier preventing digital pathology adoption has been a lack of widespread acceptance of digital slides as a safe alternative to conventional glass slides. Historically, validation literature investigating the safety of digital pathology as an alternative to conventional light microscopy has focussed on concordance metrics of glass and digital diagnoses, when arguably, it is appreciation of discordant cases that provides the clinical pathologist with the best opportunity to evaluate the scope of safe digital practice in their specialty. Chapter 3 describes a novel study to analyse diagnostic accuracy of whole slide imaging and identify key training and educational targets for novice digital pathologists.

Chapter 4 presents the validation and training protocol developed by the author for Leeds Teaching Hospitals NHS Trust, which was subsequently adopted by the Royal College of Pathologists as an example of best practise in digital pathology implementation.[1] Chapter 5 describes the deployment of this protocol to train and validate the primary digital diagnosis of cohorts of breast and neuro- pathologists. Chapter 6 introduces modifications of the protocol for use for more niche reporting scenarios: frozen section diagnosis and immunohistochemistry assessment. Chapter 7 responds to concerns in the pathology community regarding accreditation of digital services, and the use of WSI for primary assessment of screening programme specimens.

The body of work presented in this thesis has generated multiple peer reviewed publications which have influenced national and international digital pathology guidance. In this time period, enormous progress has been made in converting digital pathology from a niche technology for the early adopter to a mainstream topic at clinical digital pathology conferences, and the number of deployments and planned deployments in the National Health Service and beyond has risen dramatically. The use of digital slides in routine clinical practice represents a major departure from conventional light microscopy working practices, and the author hopes this work will help the pathology community maintain diagnostic quality in a time of change.

Table of contents

Statement of inclusion of work from jointly authored publications……..3

Acknowledgements……..4

Abstract……5

Chapter 1 Clinical Digital Pathology – Background, Barriers and Benefits……13

- **1.1 Digital pathology: the technology……14**
- **1.2 Clinical uses of digital pathology……..16**
- **1.3 Deployment strategies……20**
- **1.4 Strategic context……24**
- **1.5 The benefits of digital pathology adoption……28**
- **1.6 Financial benefits of digital pathology……40**
- **1.7 Future perspectives - image analysis and artificial intelligence……46**
- **1.8 Barriers to adoption……46**
- **1.9 Conclusion……52**

Chapter 2 Digital Pathology Access, Usage and Attitudes in the United Kingdom...54

- **2.1 Introduction……54**
- **2.2 Aim……54**
- **2.3 Methods……54**
- **2.4 Results……55**
- **2.5 Discussion……63**

Chapter 3 Evaluating the evidence for the safety of primary digital diagnosis……67

- **3.1 Introduction……67**

- **3.2 Materials and methods……..69**

- **3.3 Results……74**

- **3.4 Discussion……82**

Chapter 4 Developing a training and validation protocol for primary histopathological diagnosis using digital pathology……87

- **4.1 Background……87**

- **4.2 General principles and overview……..88**

- **4.3 The protocol phases in detail……..91**

- **4.4 Conclusion……..95**

Chapter 5 Validation in practice……98

- **5.1 Primary diagnosis of breast histopathology……99**

- **5.2 Validation of neuropathology for primary diagnosis……116**

- **5.3 Conclusion……129**

Chapter 6 Validation of digital diagnosis for non-primary diagnostic use cases…..132

- **6.1 Frozen section assessment……132**

- **6.2 Immunohistochemistry assessment……135**

- **6.3 Conclusion……143**

Chapter 7 Maintaining quality and safety with digital diagnosis……144

- **7.1 ISO accreditation for digital pathology services……..145**

- **7.2 Clinical and diagnostic considerations……153**

- **7.3 Digital pathology and patient safety for cancer screening……163**

- **7.3 Conclusion……175**

Chapter 8 Conclusion……176

List of abbreviations……184

References……185

-

List of Figures

Figure 1. Leeds Virtual Microscope – an example of digital slide viewing software....10

Figure 2. Example of a phased deployment with gradual accrual of benefits.....17

Figure 3. The benefits of digital pathology.....30

Figure 4. The benefits of digital pathology can be appreciated at multiple levels.....41

Figure 5. Access to and ownership of digital pathology hardware.....58

Figure 6. Current usage of digital slides.....59

Figure 7. Projected usage of digital slides.....60

Figure 8. Perceived benefits of digital pathology.....62

Figure 9. Perceived barriers to digital pathology.....63

Figure 10. Factors that could enable digital pathology usage.....64

Figure 11. Categorisation of pathologists.....97

Figure 12. A digital pathology workstation in use during the breast histopathology validation.....103

Figure 13. Missed diagnostic objects.....107

Figure 14. Slides that were difficult to interpret on the digital microscope.....110

Figure 15. Pathologist reporting modality preferences in V2.....112

Figure 16. A neuropathologist at work during their validation.....120

Figure 17. Example of a digital slide of Gomori stained muscle which could not be interpreted.....125

Figure 18. Example of a digital slide of a brain tumour where identification of mitotic figures was challenging.....126

Figure 19. Pathologist reported satisfaction with digital IHC training slides.....140

Figure 20. An example of a commercially available calibration slide.....153

Figure 21. Examples of suboptimal digital slides……..156

Figure 22. Assessment of a sentinel lymph node on the digital microscope……..159

Figure 23. The author delivering a session on digital pathology implementation at one of the Leeds Digital Pathology Workshops in 2018……181

List of Tables

Table 1. Respondent department characteristics……..58

Table 2. Prioritisation of digital pathology for institutions……..62

Table 3. Summary of Royal College of Pathologists system of categorisation for discrepancies……73

Table 4. Summary of Royal College of Pathologists system of categorisation of discrepancies for duty of care reviews……74

Table 5. Example of a discordance analysis for a colonic biopsy……75

Table 6. Types of discordance**……**……78

Table 7. Types of discordance classified by the Royal College system for discrepancy classification ……78

Table 8. Potential for harm in discordant case scenarios……79

Table 9. Examples of diagnostic scenarios with the potential to cause major/moderate harm ……80

Table 10. Summary of discordant dysplasia diagnoses ……81

Table 11. Discordances related to difficulty locating diagnostic objects……82

Table 12. Objects and features that caused difficulty on digital slide review……83

Table 13. Summary of the validation and training protocol for primary digital diagnosis……**……**…..92

Table 14. Training cases for breast histopathology primary digital diagnosis……107

Table 15. Specimen types included in the V2 caseload……109

Table 16. Types of diagnosis included in the V2 caseload……110

Table 17. Pathologist concordance and discordance percentages in V2……111

Table 18. Clinically significant discordances documented during V2……112

Table 19. Pathologist confidence in digital and glass slide diagnosis in V2……113

Table 20. Validation training cases for neuropathology primary diagnosis ……123

Table 21. Discordant cases from the training phase of validation……125

Table 22. Live reporting validation statistics……126

Table 23. Discordant cases from the live reporting phase of validation (V2)……128

Table 24. Pathologist diagnostic preferences……128

Table 25. Frozen section training set……136

Table 26. Summary of validation protocol for immunohistochemistry assessment……137

Table 27. Immunohistochemical stains pathologists identified as difficult to interpret at 20x magnification……143

Table 28. Potential pitfalls of digital diagnosis organized by topography……164

Table 29. Digital pathology scanning and viewing specifications – experimental data……167

Table 30. Experimental digital pathology versus light microscopy concordance data……168

Table 31. Experimental discordances encountered……169

Table 32. Diagnostic B codes for breast biopsy specimens……169

Table 33. Digital pathology scanning and viewing specifications – validation data..170

Table 34. Direct comparison digital pathology versus light microscopy validation data……171

Table 35. Discordances from direct comparison validation data……..172

Table 36. Pathologist slide viewing schedule for breast cancer screening study……173

Table 37. Intraobserver variability for breast lesion classification using digital and glass slides…….174

Chapter 1. Clinical Digital Pathology – Background, Barriers and Benefits

This chapter summarises work by the author from the following publications:

Williams BJ, Bottoms D, Treanor D

Future-proofing pathology: the case for clinical adoption of digital pathology

***Journal of Clinical Pathology* 2017;70:1010-1018.**

Williams BJ, Bottoms D, Clark D*, Treanor D.*

Future-proofing pathology part 2: building a business case for digital pathology

***Journal of Clinical Pathology* 2019;72:198-205.**

Digital pathology (DP) is a technology by which conventional glass microscopy slides are scanned using a high quality microscope lens to capture a digital whole slide image (WSI). These digital images are stored, transmitted and shared, and can be viewed and annotated by a pathologist on a computer screen using specialised slide viewing software. The transferability and flexibility of digital slides has led to widespread use of DP for education and research purposes in the healthcare sector and higher education. [2-4] More recently, healthcare providers have expressed increasing levels of interest in complete or partial digitisation of digital pathology in diagnostic settings.

In the clinic, early adoption of WSI systems has largely focussed on secondary diagnosis (e.g. for second opinions and frozen diagnosis), with only a few centres utilising DP for large scale, routine primary diagnosis, including sites in Sweden, the Netherlands and Canada. [5-7] WSI systems have been European Conformity (CE)

marked for primary diagnostic use in Europe for many years, and during the course of this work the Food and Drug Administration (FDA) has announced approval for marketing of two WSI devices for primary diagnosis in the United States.[8, 9] These regulatory milestones have accelerated interest in digital deployment for primary diagnosis.

In this chapter, the fundamentals of WSI technology and its deployment are described, in addition to a detailed list of proposed clinical uses for digital pathology. The strategic context of digital pathology adoption is discussed, and the key benefits of and barriers to clinical DP implementation are reviewed.

1.1 Digital pathology: the technology

Whole slide imaging systems are commercially available from a range of different vendors, but all systems share common imaging workflows that allow digitisation, storage and transfer of high resolution digital images of glass slides. The work contained with this thesis almost exclusively utilises scanning hardware from Leica Biosystems, (predominantly Leica AT2, *Leica Biosystems, Vista, CA, US*) and the imaging workflow for this system will be described.

1.1.1 Pre- imaging, focussing and image acquisition

Firstly, glass slides are manually loaded into the scanner in slide racks, either singly, or in batches of up to 400 slides per scanner. Low resolution cameras inside the scanner acquire low power “snapshots” of the slide and slide label. The low power

image of the slide is analysed by an inbuilt algorithm to detect tissue on the slide. Image focus points are applied to the detected tissue in a mesh-like network. A single high resolution image of each focus point is acquired, and an algorithm detects the optimal plane of focus in the z axis for each focus point. This process generates a map of the optimal focus planes for that slide. This map is then used to acquire the WSI using microscope objective lenses of 20x or 40x magnification, resulting in effective resolutions of 0.2 to 0.5 microns per pixel. Slides are illuminated by a light source beneath the scanning stage, and the microscope lens is moved across the static slide to capture serial images of the slide. In the Leica system, these images are acquired in stripes in the y plane.

1.1.2 Image processing, storage and viewing

The image is then processed so that image stripes are stitched together, and the image can be sharpened. The resulting image files are compressed to produce more practical file sizes for transfer and storage. Images are stored on a file server, and image management database software is used to access the images. The images can be viewed on the computer screen using software which allows the pathologist to pan through tissue, zoom in and out, make digital measurements, and add annotations. An example of this software, the Leeds Virtual Microscope [10], can be seen in figure 1.

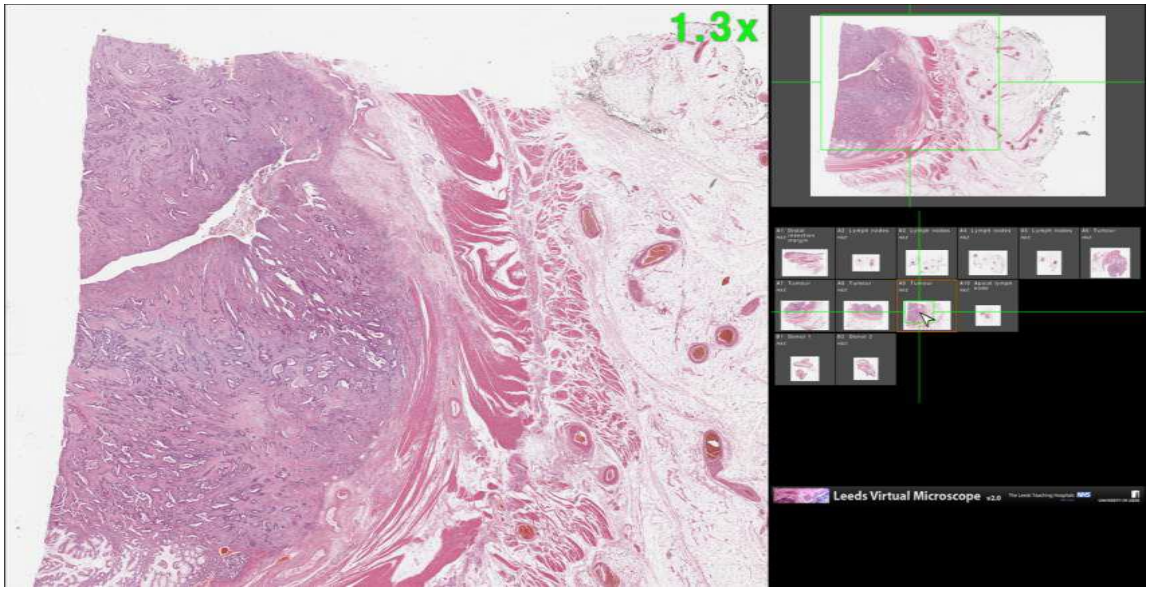

Figure 1. Leeds Virtual Microscope – an example of digital slide viewing software[10]. The entire slide tray can be viewed on the bottom right, with a thumbnail of the selected slide above. The magnified view of the selected slide is navigated on the left.

1.2 Clinical uses of digital pathology

The transferability and flexibility of the digital slide format lends itself to a number of different use cases, supporting different areas of the pathology workload and workstream, all of which represent varying degrees of clinical "risk". These use cases are identified and clarified in this section.

1.2.1 Primary diagnosis of pathological specimens

This is the replacement of conventional light microscopic examination of glass slides with examination of whole slide images on screen by a pathologist to make a diagnosis as part of their standard diagnostic workflow. A diagnostic department may decide to use digital pathology for the primary diagnosis of the entirety of its workload, or may select individual histopathology subspecialties (eg, breast pathology) or an individual histopathologist's workload to digitise. Kalmar and

Linköping Hospitals in Sweden were early adopters of digital pathology, with slide scanning fully integrated into laboratory workflow, and primary diagnosis made on digital slides by a proportion of their pathologists.[7] Primary histological assessment of diagnostic and therapeutic specimens can provide definitive diagnosis, grading and staging information, and direct medical and surgical management of a patient, and thus primary diagnosis represents the highest risk "use case" for DP.

1.2.2. Assessment of immunohistochemistry (IHC)

This is the replacement of conventional light microscopic examination of glass slides with examination of whole slide images by pathologists to assess immunohistochemical stains. Such immunohistochemistry slides are often secondary/ancillary tests, which do not form part of the initial laboratory or diagnostic workflow for a case. Reconciling these secondary studies with the original histology can be time-consuming, and the immunohistochemistry slides may be reported by the initial pathologist that requested them, or by a second pathologist. These tests can help refine diagnosis, suggest the origin of a metastatic tumour, or direct therapeutic management.

1.2.3 Multi-disciplinary team meetings (MDTM) /tumour board

This is the selection, collection, review and presentation of whole slide images or annotated regions of interest of cases for discussion at multidisciplinary meetings/tumour boards with clinicians, radiologists and other healthcare professionals to review diagnosis and prognosis and direct patient management.

1.2.4 Frozen section diagnosis

This is the use of whole slide images to provide rapid, intraoperative histopathological opinion. The pathologist may be on site, or may be working remotely, particularly if the service is required out of hours. This use case for digital pathology has been successfully implemented in Canada for over 10 years, with neuropathology frozen sections reported remotely on digital slides since 2006.[5, 11]

1.2.5 Requesting second opinions

This is the use of a digital pathology system to request a second opinion on a previously examined case. Second opinions may be required:

a) within a department for difficult cases (mandatory for reporting of certain entities, eg, dysplasia in patients with Barrett's oesophagus undergoing surveillance[12])
b) within a regional network for referral and review of MDT/tumour board cases
c) from regional/national/international experts for rare/complicated cases
d) as part of quality assurance protocol within a department to audit and detect diagnostic errors.

1.2.6 Receiving second opinions/review cases

This is the use of a digital pathology system to render a second opinion on a previously examined case, for example, a case submitted for MDT/tumour board discussion, or referral of a difficult skin case from a general pathologist to a dermatopathologist.

1.2.7 Remote working

This is the use of a digital pathology system to enable diagnostic pathologists to view slides and make diagnoses from off-site locations, which may include other networked hospitals, academic institutions or home. Gävle hospital, Sweden, were able to solve a local recruitment problem by employing a pathologist to work remotely from home, receiving their workload in the form of digital slides.[13] As well as providing more flexible modes of employment, remote working may be required on a temporary basis in times of exceptional service need, when employees are unable to work in the department (e.g. during viral pandemics, or extreme weather conditions).

1.2.8 Insourcing/outsourcing diagnostic work

This is the use of a digital pathology workflow to allocate units of work across and beyond regional/national networks, or between public and private institutions to generate income, eliminate backlogs or make best use of available diagnosticians. On an international scale, digital pathology may help to broaden access to quality diagnostics, while offering income generating opportunities, a strategy already being explored at a number of centres, including the University of Pittsburgh Medical Center.[14] Similarly, time-sensitive diagnostic slides could be outsourced to trusted partners in alternative time zones to enable rapid diagnostic turnaround out of hours, without resorting to costly and inconvenient pathologist on-call rotas.

1.3 Deployment strategies

Deployment strategies are likely to vary according to the strategic context, and local constraints of the institution, but a number of common scenarios for adoption can be described.

1.3.1 Solving specific, local logistical problems

A department may find it temporarily lacks sufficient diagnosticians in a particular field, either due to staff losses or increasing workload, for example, gynaecological pathology. Introduction of a single scanner to scan all or part of the gynaepathology workload might aid the department by (a) encouraging return or retention of peri-retirement diagnosticians, who will be able to work flexibly and remotely, (b) potentially attracting new workforce applicants that are interested in working digitally and (c) enabling rapid outsourcing of work to regional partners.

1.3.2 Digitizing specific, discrete parts of the department's service

Departments may elect to digitise particular parts of their service in insolation to solve a particular local issue - for example, remote reporting of frozen section/urgent out of hours specimens. The ability to report these specimens remotely makes on call duties less onerous for the diagnostician, and could improve turnaround times of out of hours reporting, as consultants will not be required to travel to the hospital to make their diagnosis. This is an application of digital imaging already utilised in the field of radiology. The technology would also help in situations where the local specialist is not available to make a diagnosis (eg, due to illness, annual leave), and the slides can be transmitted to a regional partner.

1.3.3 Full digitisation of diagnostic services

Following successful procurement of a digital pathology solution, deployment timescales and resource allocation will depend on the scope of the investment and number of Information Technology (IT) systems that need interfacing.

The installation of scanners and pathologist workstations is relatively simple, provided sufficient space and basic infrastructure (eg. uninterruptable power supply, network points) are in situ. However, interface development, testing and "go- lives" are likely to prove time consuming and error prone, therefore planning and testing should be prioritised as early as possible in the project. [93] The major area of disruption is likely to concern the interconnectivity of systems in a multi-site deployment, which will require liaison and concerted action from network managers and information governance leads to ensure appropriate and secure information storage and exchange.

Implementation of digital pathology will have significant implications for workflow and resource utilisation, and it is crucial that working processes are examined. In NHS pathology settings, LEAN/six-sigma analysis are the methods most commonly used in the early stages of implementation. Deployment of the technology will be disruptive and pathologists' opinions of migration to digital reporting are likely to vary significantly, from those that are keen to adopt, to those that are resistant. Training and individual validation for digital pathology reporting is an important part of safe digital adoption, and should be carefully planned to ensure timescales and targets for digital reporting are appropriate. Full clinical adoption in a busy teaching hospital is likely to be a phased process over 2-3 years, at the end of which time there would

still be requirement for some, minimal light microscopy use for a limited number of situations where digital microscopes cannot be used (e.g. to examine polarisable material).

Digitisation of the diagnostic activities of a histopathology department may occur in a phased manner, allowing stepwise introduction of a number of use cases, and gradual accrual of experience with the technology. This would result in stepwise accumulation of the benefits of digitisation over a number of years. For an example of a phased deployment and the accumulation of benefits, see figure 2. Smaller, simpler changes in workflow with immediate efficiency savings, for example, second opinion cases, MDT digitisation could be prioritised early in the digitisation, with more complex, large-scale changes in practice such as use of digital diagnosis for standard primary diagnosis deferred until the laboratory, and diagnosticians have gained experience in the laboratory workflow, and the digital diagnostic process.

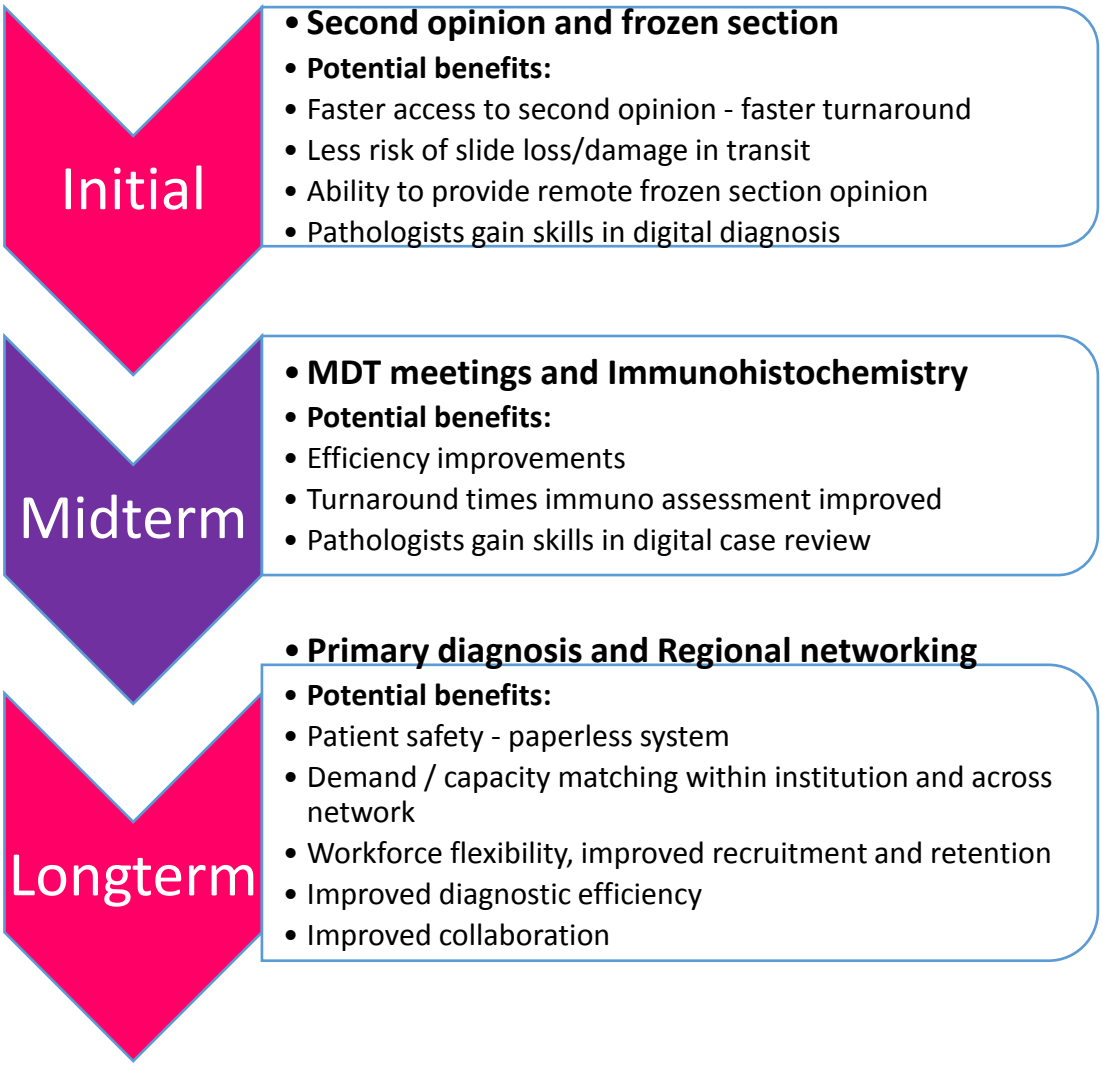

Figure 2. Example of a phased deployment with gradual accrual of benefits. Institutions can proceed stepwise from initial niche uses to complete digitisation.

1.3.4 Regional transformation projects

Digitisation may form part of larger, regional sustainability plan, with scanners and diagnostic workstations installed at a number of sites to form a regional network for collaboration, transmission of cases to MDT or for second opinion, redistribution of workload in response to fluctuations in demand and capacity. In this way, digitisation could underpin the structure of laboratory mergers and centralisation of laboratory services.

1.4 The Strategic Context

Diagnostic pathology services in the United Kingdom, and worldwide, are facing unprecedented challenges as they strive to provide quality, timely diagnoses against a background of increasing services pressure. In this section, the strategic context of digital pathology adoption is discussed.

1.4.1 Increasing Volume and Complexity of the Workload

Clinical pathology departments face the universal challenge of increasing workload, in terms of both case volume and case complexity. In the UK, year on year, the volume of cellular pathology requests received by laboratories has increased by an average of 4.5%.[15]The drive to identify pre-cancerous conditions and early stage cancers adds to the complexity of histopathological assessment, when morphological clues can be subtler and more time consuming to interpret.

In addition to an increase in specimen requests, the pathologist is required to take more tissue slides and create more slides for each cancer diagnostic and therapeutic specimen. These extra slides are required to satisfy the requirements of increasingly detailed minimum data sets for cancer reporting published by the Royal College of Pathologists (RCPath) and the College of American Pathologists (CAP).[15] In parallel with this, the arsenal of adjunctive immunohistochemical and molecular tests that can refine diagnosis, prognosis and therapeutic decision making expands year on year, again requiring more input from the pathologist.

1.4.2 Specimen Turnaround Times and Targets

The National Health Service (NHS) already imposes challenging turnaround targets for the investigation of possible cancer, with the 2015 report of the Independent Cancer Taskforce proposing even higher standards, proposing that in 2020, 50% of patients referred for cancer testing by their general practitioner (GP) should have their definitive diagnosis within 2 weeks, and 95% within 4 weeks. [16]

1.4.3 Workforce crisis

Against this background of escalating diagnostic workload, pathology is in the midst of an emergent workforce crisis. In the USA, it is predicted that the number of practicing pathologists will have declined from 5.7 to 3.7 per 100 000 people between 2010 and 2030.[17] In the next 5–10 years, there will be a similar shortage of consultant pathologists in the UK across all subspecialties. Data from the Royal College of Pathologists show that 32% of cellular pathologists are over the age of 55 (615 people), and are expected to retire in the next 5 years.[15] Meanwhile, from August 2015 to June 2016, only 52 trainees in histopathology were recommended to the General Medical Council for completion of training. Waiting times are starting to increase as a result of increasing mismatch between staffing

capacity and demand.

1.4.4 The need to increase capacity

In the USA, it is predicted that pathologist workforce demand will have increased by 16% by 2030,[17] while numbers of pathologists per capita decline. In their November 2016 publication, 'Testing times to come? An evaluation of capacity in pathology',[15] Cancer Research UK highlights the need to ensure pathology services maximise efficiency, with networking and consolidation of pathology services prioritised. In light of increasing costs for staff overtime and outsourcing, optimisation of the pathology workforce is vital. Improved retention of near-retirement consultants, and increased efforts to drive recruitment in medical schools have been proposed, but these measures are not sufficient to solve the problem. The report recommends that departments and trusts should invest in infrastructure to support digital pathology, and that on-screen examination of histological slides should be used to enable more efficient networked services. This sentiment is echoed in the Nuffield Trust's publication 'The Future of Pathology' which states that 'without change it will be difficult to maintain an adequately skilled workforce in many areas of the country'.[18] The Life Science Industrial Strategy suggests that systematic digitisation of pathology images could be readily established providing substantial efficiencies in the pathology service within the NHS, allowing the system to become increasingly virtual and reducing the need for every hospital to have the full on-site set of pathologists. Whilst the strategy serves as a recommendation to government rather than formal policy, NHS England appears to support the recommendations.[19]

1.4.5 The drive towards networks and service mergers

In the UK, the two Carter reviews of pathology, of 2006 and 2008 both recommended the formation of networked pathology services, with centralisation of laboratory resources, and the development of 'hub and spoke' local networks. [20, 21] More recently, the report by Lord Carter into operational productivity in the NHS suggested further consolidation and collaboration between services, stating that 'Our further analysis has confirmed that consolidated pathology organisations are the most efficient in the NHS'.[22] Digital pathology offers an enabling platform for centralised slide production, with dispersal of diagnostic pathologists across or between regions. Digital imaging has the potential to assist trusts in the flexible use of clinical pathologist expertise in relation to laboratory locations, pathologist offices and MDT inputs. In their paper, 'Can Digital Pathology Result In Cost Savings? A Financial Projection for Digital Pathology Implementation at a Large Integrated Health care Organization', Ho *et al* describe how a digital pathology system would enable enterprise wide reporting of specimens, while allowing laboratory services to consolidate from 20 dispersed hospitals to two centralised sites.[23]

1.4.6 The drive towards digitisation of healthcare

As part of the Five-Year Forward View, the Independent Cancer Taskforce Strategy's paper, 'Achieving world class outcomes; a strategy for England 2015–20' highlights a drive towards achieving earlier diagnosis, the need to invest to deliver a modern, high-quality cancer service and the importance of training staff to realise advances in technology.[16, 24] The National Information Board's Framework for Action 'Personalised Health and Care 2020', similarly emphasises the importance of

improving access to healthcare records, implementing personalised medicine, supporting innovation and getting best use from technology. Digital pathology can take medicine a step further towards the information governance target of a 'paperless' healthcare system.[25] The National Advisory Group on Health Information Technology's paper 'Making IT work—harnessing the power of health information technology to improve care in England' (August 2016) states the Five Year Forward View aims will not be met without prioritising digitisation of services, and that digitisation is likely to reap safety and quality improvements, concluding that 'the one thing the NHS cannot afford to do is to remain a largely non-digital system, it is time to get on with IT'.[26]

1.5 The benefits of digital pathology adoption

The principal perceived benefits of adoption of digital pathology can be broadly divided into four domains: improving patient safety, improving diagnostic workflow, improving workforce factors and improving service quality, with improvement in any one domain likely to contribute to improvement in all other domains, and benefits felt at multiple levels from patient to region. (see figures 3 and 4)

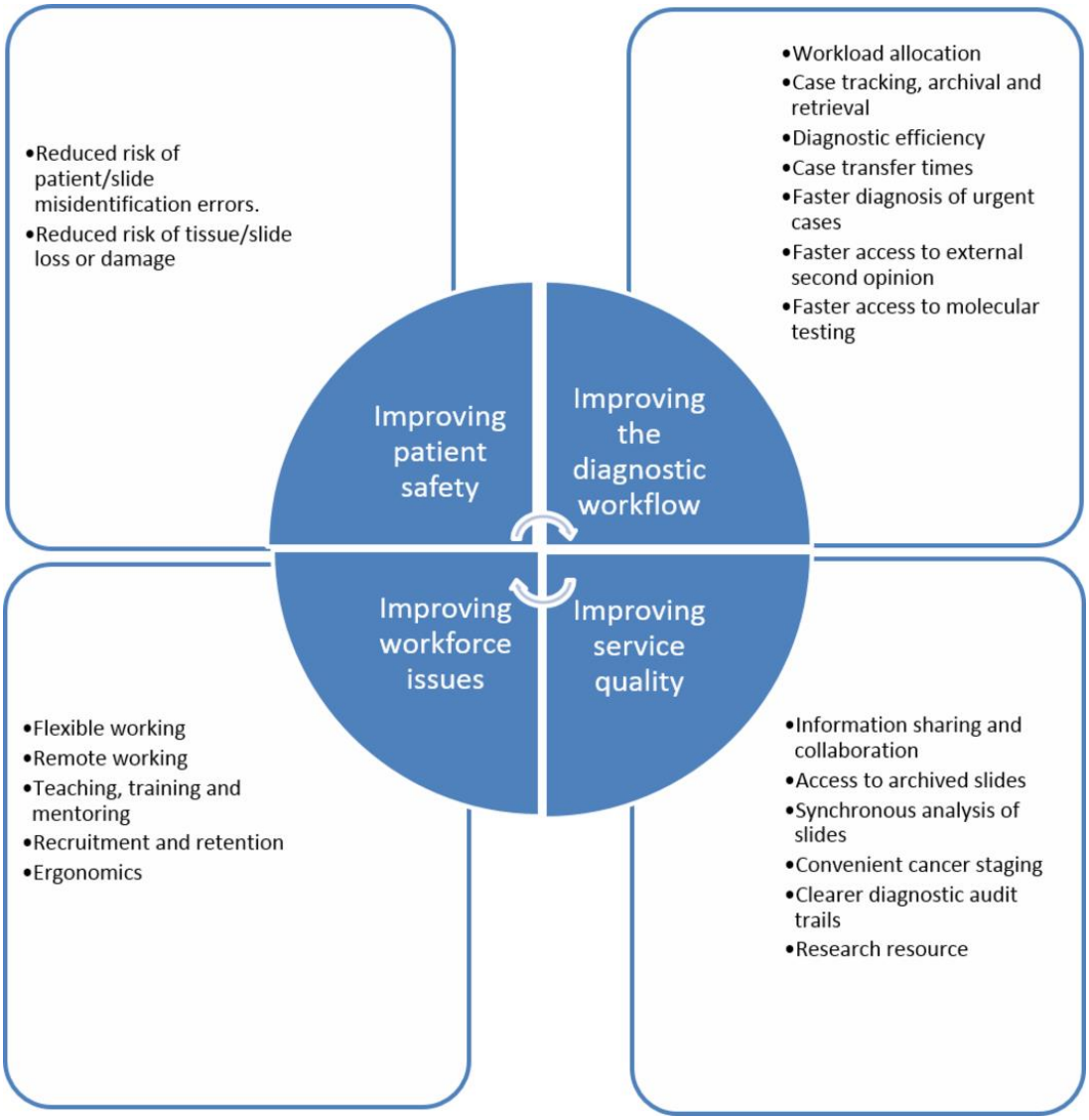

Figure 3. The benefits of digital pathology, reproduced from Williams BJ, et al. J Clin Pathol 2017[27]. Benefits can be divided into those that improve the diagnostic workflow, service quality, workforce issues and patient safety.

1.5.1 Improving patient safety

1.5.1.1 Reduced risk of patient/slide misidentification errors

The use of an integrated digital pathology system, with paperless transmission of digital slides directly to the pathologist significantly reduces the possibility of a misidentification or transposition error (eg, mixing up slides from two patients). These are potentially the most serious errors that can originate in the diagnostic laboratory, with an incidence estimated at 1%.[28] Digitisation of prescription

practices, with the introduction of e-prescribing lead to a significant reduction in the relative risk of medication error of 13%–99%.[29] A fully digital end to end pathology workflow would remove the majority of manual patient identification checks which are prone to human error.

1.5.1.2 Reduced risk of tissue/slide loss or damage

Potential loss and damage of valuable patient tissue on glass slides is a risk faced by laboratories on a daily basis as they transport glass from the laboratory to the diagnostician, from the feeder hospital to the regional cancer centre for review, or from the general pathologist to the recognised expert. Digital slides provide a portable, instantaneously transmissible diagnostic image which does not fade or degrade, and is not subject to the transport risks faced by glass slides.

1.5.1.3 Enhanced safety features of digital reporting

Digital pathology slide viewing software can incorporate a number of additional safety checks to aid the pathologist, including computerised reminders if slides, or tissue regions have not been reviewed by the pathologist before case sign-out. [27]

1.5.2 Improving the diagnostic workflow

1.5.2.1 Workload allocation

A digital pathology system offers the flexibility and agility for streamlined ‘pushing’ and ‘pulling’ of cases to and by pathologists to respond to fluctuations in workload or case mix in a department. Digital slide management software can allow the

entirety of a pathology workforce access to outstanding or backlogged work, enabling pathologists with extra capacity to ‘pull’ pool cases.

Conversely, a digital pathology system also allows for expedited ‘pushing’ of cases from a pool, or between pathologists, to ensure cases are promptly transferred to the most appropriate diagnostician within a network, or across a region. Enabling flexible workload distribution, both within an institution and across a network allow for closer capacity-demand matching and a more lean approach to achieving the requisite diagnostic output for a population.

1.5.2.2 Rapid case tracking, archival and retrieval

In the conventional laboratory with glass slide diagnostics, trays of slides and request forms are delivered to and transferred between a variety of locations within the laboratory and the diagnostic department. There are ample opportunities for slides to get mislaid, and urgent sourcing of a glass slide can be time consuming for clerical and diagnostic staff. A digital system ensures that a crucial or time-sensitive case can be accessed instantly, by any registered user, should the need arise. Review of previous specimens can be vital in cases such as the assessment of progressive disease or evaluation of a new tumour in a patient with cancer, and is likely to improve the quality of the pathologists’ assessment of a live case. The storage of digital slides allows for instant retrieval and review of cases, a process which is time consuming and inefficient using conventional glass slide archives.

1.5.2.3 Increased diagnostic efficiency

One time and motion study identified potential for a 13% time saving in pathologist diagnostic efficiency with digital slide reporting, with efficiency gains in the organisation of, querying, matching and searching of cases. [30]In addition, a limited number of diagnostic centres and individual diagnosticians have reported increased diagnostic efficiency using digital microscopes versus conventional light microscopes.[31] These improvements relate to a number of specific areas, including rapid availability of images, faster on-screen measurements and annotations of slides and ability to multitask while using a computer screen for diagnosis, instead of switching between the microscope and the PC. In addition, pathologists do not have to physically load and unload microscope slides, compare glass slide labels with paper request forms or refocus their microscopes for tissue of different thicknesses.

While the existing literature shows promise, more work is needed in terms of large-scale clinical deployments before there is sufficient evidence to support improved diagnostic efficiency.

1.5.2.4 Reduced case transfer times between the laboratory and the diagnostic pathologist

Current glass slide dependent processes rely on delivery or collection of assembled cases of glass slides from the laboratory, an inefficient process requiring time and manpower, which risks loss or damage of slides. With a digital pathology system, slides are instantaneously accessible to diagnosticians without the need for physical case assembly and delivery.

1.5.2.5 Faster diagnosis of urgent cases

Prioritisation of urgent cases can be difficult to manage using conventional glass slide processes, and is often reliant on manual tagging or labelling of specimens as urgent. This can be difficult to do when slides are in transit, in pools or on pathologists' desks. Recategorisation or escalation of case urgency is difficult and time consuming. Digital pathology allows easy flagging and escalation of priority of cases, and enables the laboratory administrator to 'push' the most urgent cases to the top of pathologist's worklists, without the need for explicit communication.

1.5.2.6 Faster access to external second opinion

Substantial numbers of slides are transferred between hospitals, either as submissions for MDT discussion at regional cancer centres, or for second opinion of difficult or rare entities from recognised specialists. Faster second opinion referral times of these cancer specimens are likely to lead to increased use of second opinions, and improved quality of cancer diagnosis and care. The Royal College of Pathologists recommends that all pathologists should actively participate in referral practice as this is in the best interests of patients, good continuing professional development and good practice, and that financial considerations should not be a deterrent to referral.[32]

1.5.2.7 Faster access to molecular/ancillary testing

Digital pathology provides a platform for parallel specimen workflows between histopathology and molecular medicine. When the pathological assessment of a case is liberated from stained tissue on glass, the glass and tissue can be expedited to

molecular medicine where appropriate, converting a sequential histopathology—molecular workflow to a more efficient parallel process. Digital pathology allows rapid tumour annotation and cellularity assessment for downstream microdissection.

1.5.3 Improving workforce factors

As discussed previously, pathology departments are facing unprecedented workforce challenges, which digital pathology could improve in a number of ways.

1.5.3.1 Platform for flexible working

Digital pathology offers the potential for more flexible patterns of work for pathologists, freeing the diagnostician from geographical and temporal restraints on where and when they can work. In this respect, it can help to optimise the working hours of the workforce, helping those working less than full time to maximise the hours they can offer and providing an incentive for those considering retirement to continue to offer their services on more flexible terms.

1.5.3.2 Platform for remote working

The ability of digital pathology to support working from remote locations has the potential to optimise the existing workforce by allowing the pathologist to make efficient use of their time, regardless of the location at which they are based, for example, allowing them to review their MDT cases from University locations, allowing regional ‘spokes’ to take on extra work from ‘hub’ institutions when there are backlogs, etc. This mode of working can also help cover temporary staffing issues,

for example, allowing local colleagues to cover specialist reporting during periods of illness/annual leave.

1.5.3.3 Improved teaching, training and mentoring

Improved access to, and sharing of instructive and unusual cases is likely to prove of great benefit to undergraduate and postgraduate education, histopathology training and continuing professional development. Access to quality teaching cases can vary within and between departments. Digitisation and subsequent anonymisation of pathology images for a local teaching/training archive would provide an excellent resource for a department. In addition, the ability to view digital cases simultaneously allows a trainer and any number of trainees to share cases in real time, so the trainee and trainer can receive instantaneous feedback on a case.

1.5.3.5 Recruitment and retention

The inherent flexibility of a digital pathology diagnostic system should help to future-proof histopathology, allowing the workforce to offer their skills in a variety of ways. As well as aiding retention of staff peri-retirement, the perceived 'revolution' from light microscopy to digital microscopy could help to rebrand histopathology as a modern, innovative and exciting field for junior doctors to work in. The ability to work from remote locations may be particularly helpful in recruiting to traditionally hard-to-staff geographical regions or subspecialties.

1.5.3.6 Ergonomic advantages

One of the largest implementations of digital pathology to date was initiated to improve workplace ergonomics, because a member of staff was unable to perform conventional microscopy due to neck pain. [7] Conventional microscopy is linked to a range of workplace-based morbidities including neck and back problems.[33]Digital pathology allows greater diversity in working positions for pathologists, as neck position does not have to be fixed, and a range of ergonomic input devices can be used, tailored to pathologist preference and any existing musculoskeletal problems. Further work is needed to understand the long-term ergonomic and other health effects of using digital pathology display equipment.

1.5.4 Improving service quality

1.5.4.1 Improved information sharing and collaboration

As already discussed, digital pathology allows for streamlined sharing of images, both within and between departments, allowing rapid access to second opinion, or double reporting of difficult cases. In a study by Manion *et al*, in which over 5000 referral cases were reviewed and reported by a second pathologist, 11.3% of reviews had minor or major differences in diagnosis with the original diagnosis and 1.2% of all reviews would have resulted in a change in patient management. [34] A survey of laboratories in the USA noted that 6.6% of all histopathology cases were reviewed before sign out, suggesting second opinions are often obtained in clinical practice, especially in challenging areas such as breast disease.[35]Digital pathology renders second opinion and double reporting of specimens faster and more efficient, which

may help lower the threshold for seeking a second opinion, improving the quality of diagnosis and patient care.

The Royal College of Pathologists tissue pathways for gastrointestinal disease state that double reporting of slides is advisable in cases of dysplasia in inflammatory bowel disease, dysplasia in Barrett's oesophagus and cancers from bowel cancer screening patients. [12]Digital slides are easily marked and annotated, further speeding up the process of obtaining an answer to a specific question, for example, are these cells in a blood vessel? If the process of sharing cases is made simpler, it is likely that pathologists will reduce their threshold for sharing cases, which may lead to better quality diagnosis for the patient.

The introduction of biomedical scientist prereporting and screening also requires double reporting during training, and pathologist review of certain cases, which could be expedited with digital pathology.[36]

1.5.4.2 Improved access to archived slides

As discussed previously, streamlining access to a patient's previous histology is likely to lower the threshold for pathologists to review previous specimens, with the potential to improve the quality of the diagnosis for that particular patient.

Direct comparison of a current tumour biopsy with a previously resected tumour from the same patient may allow the pathologist to avoid costly further immunohistochemical investigation of the new tumour.

1.5.4.3 Ability to perform synchronous analysis of slides

Multiple digital slides can be viewed simultaneously on one screen, allowing synchronised assessment of conventional H and E histology with multiple immunohistochemical stains or special stains. The images can be aligned and locked in the same position, making assessment of complex stains and their distribution in tissue far more accurate and simple to perform. The time to physically load and unload multiple glass slides for a relatively rapid assessment (of gross tumour positivity or negativity) is a significant part of the task of immunostain scoring process, suggesting that this task could be more rapid with a digital platform.

1.5.4.4 More convenient cancer staging

Minimum datasets for cancer cases required careful measurement of tumour volume and surgical margins. These measurements often form the basis of tumour staging, and can dictate further treatment decisions for the patient. Making measurements on the light microscope is time consuming, and there can be considerable interobserver variability in measurements taken by different pathologists. Digital slide viewers can use on-screen measurement tools which enable multiple measurements to be made and recorded in a few keystrokes or mouse clicks. More accurate and reproducible measurement of tumour size and margin status will allow more accurate staging of tumours, and the selection of more effective treatment options for patients.

1.5.4.5 Clearer diagnostic audit trails

Digital pathology software allows for automatic and comprehensive diagnostic audit trails including data on who has viewed slides, when, where and for how long. It also facilitates annotation of regions of interest, which have formed the basis of a diagnosis. Some systems also incorporate these images of these regions of interest into the pathology report.[27]

1.5.4.6 Research and development opportunities

A digital pathology image archive represents a valuable resource, with diagnostic images made readily available for research purposes. Rapid transfer and availability of diagnostic slides will encourage collaboration and pooling of resources between diagnostic departments and higher education facilities, facilitating participation in national and international studies and clinical trials. In addition to providing rapid access to slides for academic purposes and clinical trial review, large volume databases of digital slides can be used in the development of new computerised algorithms for the rapid detection of new quantitative diagnostic and prognostic markers in tumours.

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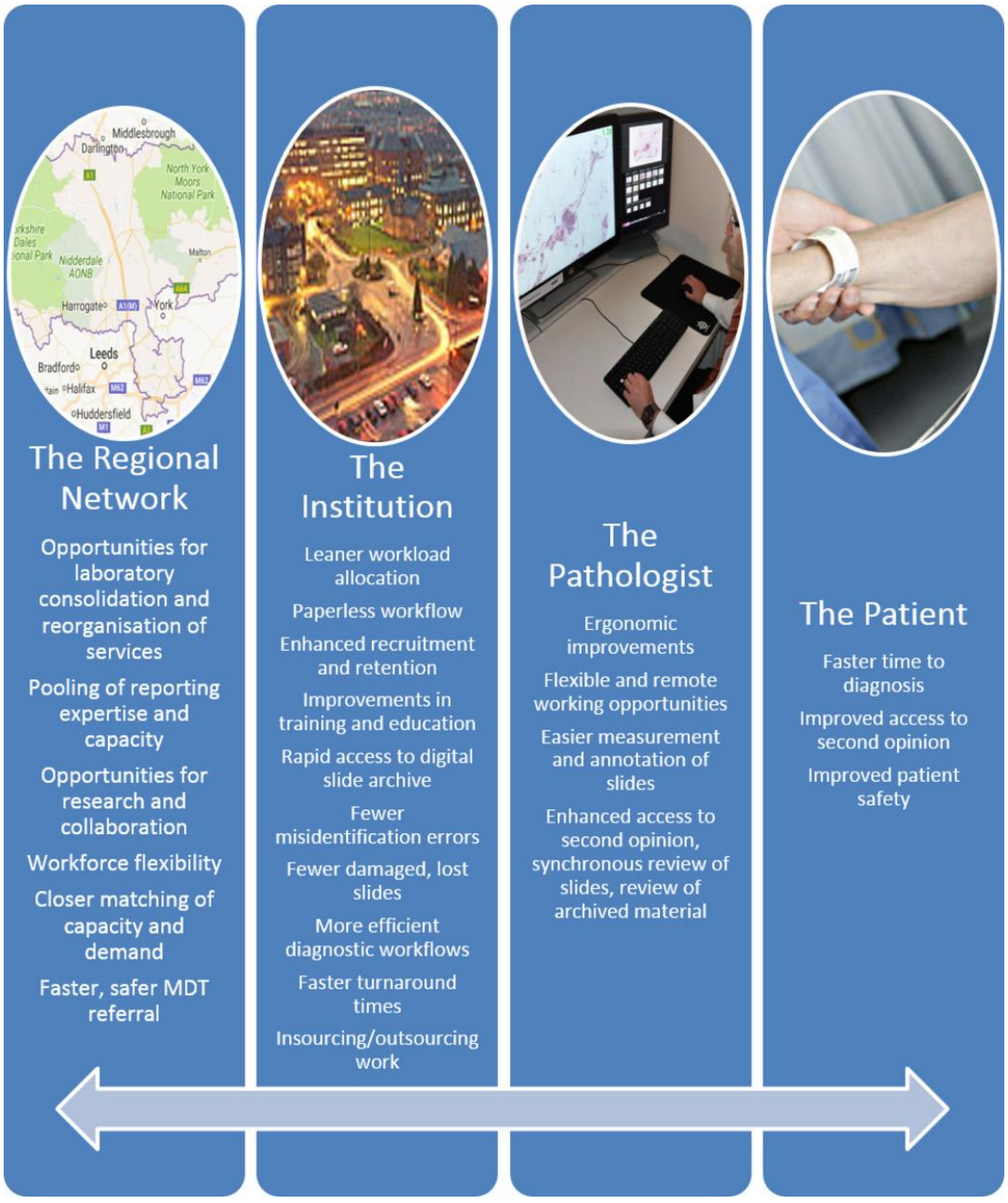

Figure 4. The benefits of digital pathology can be appreciated at multiple levels. Reproduced from Williams BJ, et al. J Clin Pathol 2017[27] The individual patient, the pathologist, the institution and the region can all potentially gain from deployment.

1.6 Financial benefits of digital pathology

In addition to quality and service benefits, there are a number of potential financial benefits for the clinical pathology department, although there is little published evidence to support these at present.

1.6.1 Potential cost savings

1.6.1.1 Locum pathologist costs

Locum pathologists are still widely used by many NHS Trusts to cover shortfalls in manpower due to retirement, maternity and carer leave, long-term sick leave, and so on. The overall cost of this is substantial (£140 per hour). Improved productivity and utilisation of the existing pathologist workforce using digital pathology, allied with easy transferability of cases should substantially reduce reliance on locum cover.

1.6.1.2 Reduced costs of referral to commercial laboratory services

Considerable sums (estimated at £35 per case) are spent by many NHS Trusts in order to keep abreast of their workloads. The turnaround times of cases outsourced to agencies can be prolonged, given the need for work to be physically transported elsewhere.

1.6.1.3 Transport savings on tissue/slide exchange between institutions/sites

There would be reductions in the logistical costs of relay of slides to reference sites for second/specialist opinions and their subsequent return.

1.6.1.4 Microscope/camera purchase

Consultant pathologist microscopes currently cost around £25,000 each. If cameras are also added this can rise to £30,000 and height-adjustable benching to provide the appropriate ergonomic posture for microscopy can add further costs. Although they have a long 'shelf-life' it has been common practice in many hospitals to provide new consultant pathologist staff with a new microscope to ensure the stock of the department is refreshed. Such regular purchases would no longer be necessary.

1.6.1.5 Reduced slide archiving and retrieval costs

Although unlikely to have an impact initially, it is highly likely that costs associated with slide/tissue storage may be avoided in the future. Where these are off-site and commercially supported these costs are not insignificant.

1.6.1.6 Reduced staff travel costs

The technology provides consultant pathologists with the ability to work at a distance from their laboratories/MDT meeting venues. This could include agile home-working (to cover future 7-day working initiatives) and satellite site working (for MDT attendances).

1.6.2 Cost avoidances

1.6.2.1 Reduced financial penalties

Avoidance of financial penalties due to cancer breaches relating to delays in obtaining pathological diagnostic opinion (currently £1000 per cancer breach[47])

1.6.2.2 Reduced litigation costs

Although cases are rare, where institutions have been prosecuted due to diagnostic error relating to pathology, these have proved to be extremely expensive. Post-event analysis has shown that such cases could often have been avoided had there been improved quality assurance checking, often including a second/ specialist opinion. Apart from the financial aspects, the reputational damage to the institution and the pathology departments can also be severe.[47]

1.6.2.3 Earlier diagnosis of disease

Digital imaging can provide quicker turnaround times for cases that require referral to external institutions for regional MDT review, which could result in cost-savings related to treatment costs and hospital stays.

1.6.2.4 Time savings for pathologists

There are indicative data suggesting productivity improvements for pathologists when they have adopted digital imaging of between 10% and 15%.[30] Specific areas where time is saved relate to immediate availability of slides without need to wait for delivery, faster measurements and annotations and easier preparation and compilation of cases for MDT meetings.

1.6.2.5 Delayed clinical workforce expansion costs

As cancer workloads continue to grow, hospitals need to expand their pathologist workforce and are experiencing recruitment difficulties. Increased productivity of the existing workforce will help offset these pressures. Applied conservatively this might give an expectation that institutions would be able to absorb an additional workload of at least 5%. Consultant annual workload is roughly estimated to be approximately 3000 cases. A 5% increase in capacity would equate to an extra 150 cases per annum per consultant for the region. Theoretically at least this could increase the number of cases that could be examined by the overall existing pathologist workforce of our region by as much as an additional 12,000 cases per annum.

1.6.2.6 Delayed laboratory workforce expansion costs

Considerable laboratory staff time is undertaken to support current ways of working that could be significantly reduced if digital imaging were adopted. These are as

follows: case assembly, case retrieval, case filing, packing and unpacking dispatched slides, time spent chasing missing/ overdue slides, time re-cutting/re-staining lost/damaged slides, time delivering slides to consultants.

1.6.3 Potential income generation

Digital slides create the ability for sites to provide remote clinical diagnosis from images generated anywhere, and will open up insourcing opportunities. Pathologists could undertake work for other institutions within the region, and there is also a market nationally and internationally.

1.6.4 The commercial case

Digital pathology is already recognised as a having a key role to play in the future of health services, and many NHS suppliers have already formed commercial partnerships with scanner, software and biomarker supplier to offer complete digital solutions, which could integrate with Laboratory Information Systems (LIMS) and electronic patient records. These partnerships may be broadened to include image access and storage solutions, such as vendor neutral archives, where pathology images could be stored alongside radiology images, photographs, electocardiogram traces etc.

Pathology services in the UK are increasingly utilising managed service contracts for the provision of laboratory equipment, and it is likely that digital pathology hardware

will be embraced in a similar fashion, allowing for more effective use of finance, and allowing for hardware refreshment as contractual periods approach their end points.

A digital pathology scanning and reporting solution also offers a platform for the use of spin-off technologies, including computer assisted scoring of immunohistochemistry and triaging of specimens.

1.7 Future perspectives – image analysis and artificial intelligence

The field of digital pathology is progressing rapidly, with innovative diagnostic and prognostic tools on the market and in development, with the potential to lead to further benefits in patient care. Algorithms for detecting regions of interest, which direct the pathologist to areas of abnormality, and programmes designed to quantify immunohistochemical staining can streamline screening and triage of cases, while tools for automated mitotic counting, tumour grading and microorganism detection could remove some of the more onerous, time-consuming tasks from the pathologists workload, leaving them to engage with the more intellectually challenging areas of diagnosis and clinicopathological correlation. [93]

It is likely that in the future, image analysis of digital slides will become part of routine practice, allowing for further streamlining of the diagnostic process, and enabling junior staff and non-clinical staff to report and sign out screened and triaged cases.

1.8 Barriers to adoption

Digital pathology uptake in the clinic has followed a classic adoption curve, with initial niche applications (including remote reporting of frozen section specimens,

education, research and second opinions) followed by larger scale, broader spectrum deployment in a small number of "early adopter" clinical sites.[37] In the course of my period of PhD study, progress has been made in most of these domains, although significant implementation barriers persist and are slowing translation of DP from academia to clinical settings.

1.8.1 Lack of evidence of diagnostic equivalence with conventional light microscopy

If digital pathology is to be implemented for primary diagnosis on a large scale, regulatory bodies, both international and national; departmental heads; and individual pathologists will have to be confident that a diagnosis made on a digital microscope is equivalent to a diagnosis made by the same pathologist on a light microscope. Efforts to validate WSI diagnosis against the gold standard of conventional light microscopy have been hampered by the innate subjectivity and variability of histopathological diagnosis.

In 2016, the author undertook was part of a group which undertook a systematic review of these studies in which study quality was assessed.[38] 38 studies were identified, and reported and a mean diagnostic concordance of WSI and light microscopy, weighted by the number of cases per study, of 92.4% was observed. Of the 30 studies quoting concordance as a percentage, 60% showed a concordance of 90% or greater, of which 10 showed a concordance of 95% or greater. There was a trend for increasing concordance in the more recent studies, reflecting the evolution of hardware and software. The review found evidence to support a high level of diagnostic concordance for WSI overall, and the conclusions can be interpreted as

encouraging for a diagnostic department that is considering a primary diagnostic digital adoption. However, the review is limited by the quality of the source studies. Included studies utilised experimental methodologies that may not accurately reflect the breadth and depth of histopathological diagnosis, or the environmental and psychological factors that exist in real world clinical pathology services.

1.8.2 Lack of regulatory approval

At the time this work commenced, there was no widespread regulatory approval for the use of WSI for primary diagnosis, and many medical institutions would be uncomfortable taking on the medicolegal risks of implementing an unapproved healthcare technology. The first WSI system was CE marked for primary diagnosis in 2012[39]. The European CE mark in itself does not necessarily persuade the pathology profession that digital diagnosis is valid, although it was a step towards acceptance of technology. FDA approval is a more rigorous process, and requires a higher level of evidence. In 2017, the FDA approved the Philips Intellisite WSI system for primary diagnostic use in US, but additionally specified that pathologists must keep their microscopes for situations where, in their clinical judgment, it would be best to defer to glass slide review. Approval for a second WSI device, the Leica AT2 was granted in 2018. These approvals represent major milestones in the acceptance and validity of WSI for primary diagnostics.

1.8.3 Pathologist attitudes

Published studies of the use of digital slides tend to present positive perceptions of WSI technology, but these studies tend to be based in early adopter institutions, where clinical adoption has been accelerated by a handful of enthusiastic individuals.

There is very limited data available about the acceptability of digital pathology to general pathology audiences. A study of Canadian pathologists in 2013 found that 71% of respondents believed there was a need for digital slide telepathology in their practice, but that its use should be reserved for teaching and consultation services, with cost and image quality issues implicated as barriers to wider clinical use.[40]

One of the fears quoted by many pathologists is that digital pathology could result in loss of work, as slides can potentially be transferred anywhere in the world for diagnosis. [41] This transferability is one of the great strengths of the WSI as the mode of diagnosis, but care would need to be taken to ensure quality of diagnosis and integrity of patient data are maintained.

There are also concerns that WSI, as an enabler of AI could result in job losses for pathology consultants, or remove the need for human diagnosticians at all. Given the current shortages of human pathologists, and the relatively limited applications of AI algorithms currently in development, this is unlikely to be the case in the near future.

[42]

1.8.4 Diagnostic speed compared with the light microscope

One very practical barrier to deployment in clinical settings is the perceived inefficiency of DP versus conventional light microscopy. A survey in the United States found that whilst 59% of respondents felt the benefits of digital pathology outweighed their concerns with its use, speed of diagnosis on digital slides was a major barrier to use in the clinic. [43] A small number of studies have attempted to compare diagnostic time on the light microscope with the digital microscope, including a study in Norway suggested that digital pathology was faster than light microscopy diagnosis in some diagnostic scenarios, but the study only reported the experience of a single pathologist. [31] A study by Hanna et al with a more experimental design used eight different pathologists, and found an overall mean loss of efficiency of 19% for WSI compared with glass slides.[44]

A pathologist in the UK will have completed at least 5 years postgraduate training on the light microscope, and may have twenty or thirty years clinical experience with this diagnostic tool. Whilst the diagnostic assessment is essentially the same on the digital microscope, the interface is very different. The pathologist needs to learn to use the image management and image viewing software, how to navigate through multi-slide cases and perform small object tissue search tasks at high magnification. Initial experiences of digital reporting are likely to be slower and more cumbersome than light microscopy practice until the pathologist has reached a level of comfortable familiarity with the WSI system implemented. The user interface is another factor likely to influence diagnostic speed on the digital microscope, with

both slide viewing software design and display resolution implicated in enabling efficient diagnosis. [10]

1.8.5 Lack of training and educational support

An interview based study conducted by Randell et al questioned a sample of 12 histopathologists on their views regarding barriers to clinical usage of DP. A key concern was lack of familiarity with the technology, and lack of confidence in their diagnostic skills with this new medium. The findings emphasise the need to ensure adequate training and support and the potential benefit of allowing parallel use of glass slides and digital while pathologists are on the learning curve.[45]

1.8.6 Lack of support for digital pathology from professional bodies

The Royal College of Pathologists' position on digital pathology implementation has altered significantly within the time frame of this PhD. As recently as 2016, RCPath president Suzy Lishman stated that there was "not yet sufficient evidence to support wholesale adoption". In 2017, the College published a strategy suggesting that digital pathology offers potential efficiency and quality benefits, and advertised for its first lead for diagnostic digital pathology[1]. Following formation of a committee, the group published guidance recommendations for the implementation of DP in the clinic. Whilst the Royal College supports the safe and considered use of DP in the clinic, Public Health England (PHE), the body responsible for the UK cancer screening programmes for breast, bowel and cervical specimens does not sanction the use of

DP for primary diagnosis of screening programme specimens. [46] As screening patients are symptom free, “healthy”populations, lower levels of risk of misdiagnosis are deemed acceptable than for symptomatic patient groups, where the likelihood of disease is greater. This will be discussed in greater detail in chapter 7.

1.8.7 Financial Constraints

Deployment and running costs for a digital pathology system will vary greatly between institutions dependent on their size, workloads, workforce, existing IT infrastructure and data storage capacity.

Indicative costs suggest a stand-alone, single hospital deployment as part of a managed service contract might cost in the region of £100,000 -£200,000 per annum depending on the size of the workload, including data storage and interfaces with the laboratory information system (LIMS). These costs would be reduced if a regional purchase strategy was adopted, especially if purchase of hardware and peripherals made use of existing NHS IT suppliers on NHS framework agreements. [47]

Compensating savings could mitigate against these costs, and provide a longterm return on investment. Digital pathology fits well with national and regional funding opportunities to support the adoption of digital technologies and improved early diagnosis.

1.9 Conclusion

In an era when histopathology services are under increasing pressure to produce more work, of greater complexity and quality, in a shorter timeframe, digital pathology systems offer a flexible platform for service improvement and development. The benefits of digital pathology, in improving patient safety, improving workflows, improving workforce factors and improving service quality can be felt by all stakeholders in the process, from the patient and pathologist, through to the institution and the wider clinical network in which it operates.

Timely adoption of digital pathology offers opportunities to future proof histopathology services in a time of emergent demand: capacity mismatching. Failure to embrace technology and modernisation could compromise the ability of pathology service providers to produce accurate diagnostic work for patients.

A number of key barriers to implementation have been identified in the literature, some of which, including lack of regulatory approval and lack of support from the Royal College of Pathologists have been overcome since the start of this piece of work.

At the time of commencement of this work, it was decided it was important to identify trends in clinical digital pathology adoption, and identify the key obstacles to real world implementation. In chapter 2, the results of a nationwide survey of clinical and academic pathology departments are presented, the results of which shaped the direction of this body of work, and indicated some of the key areas where the clinical pathology community required reassurance or guidance.

Chapter 2 Digital Pathology Access, Usage and Attitudes in the United Kingdom

This chapter contains content published in:

Williams BJ, Lee J, Oien KA*, et al* Digital pathology access and usage in the UK: results from a national survey on behalf of the National Cancer Research Institute's CM-Path initiative

***Journal of Clinical Pathology* 2018;71:463-466.**

2.1 Introduction

In chapter 1, the benefits of and barriers to digital pathology implementation in the clinic were discussed. It is important to consider what progress is being made in terms of clinical uptake of digital pathology in the UK, contemporary attitudes to DP usage, and perceived barriers to digital pathology. In chapter 2, the design and results of a nationwide survey of DP are explained and discussed.

2.2 Aim

The aim of the study was to canvass the UK pathology community to ascertain current levels of digital pathology usage in clinical and academic histopathology departments, and prevalent attitudes to digital pathology. With this in mind a national survey was developed on behalf of the National Cancer Research Institute's (NCRI) Cellular Molecular Pathology (CM-Path) initiative.

2.3 Methods

A survey was written and disseminated on behalf of the membership of the technology and informatics workstream of the NCRI's CM-Path initiative. The survey comprised 15 items and assessed:

(1) access to and ownership of digital pathology hardware;

(2) current and predicted usage of digital pathology;

(3) prevailing attitudes to digital pathology.

The survey was initially circulated to the whole CM-Path membership (a research focussed group of pathologists working in clinical and academic settings) using the SurveyMonkey online survey tool (www.surveymonkey.com) with specific instructions for completion of forms. As the aim was to assess national trends in digital pathology uptake and attitudes, responses were sought at a departmental or institutional level. Where possible, departmental heads were approached and asked to complete the survey, or forward it to the most relevant individual in their department. Data were collected over a 6-month period from February to July 2017. Reminder emails were sent out during this period, and survey invitations were extended to academic and clinical pathology departments without a CM-Path member. Simple summary statistics were calculated for each questionnaire item. Not all questions were mandatory, and some questions allowed more than one response to be selected per respondent, so denominators are shown for the results on a per question basis.

2.4 Results

A total of 41 questionnaires were completed, representing 41 institutions in England, Wales and Scotland, with no duplications.

2.4.1 Respondent demographics

Respondent demographics are shown in table 1. The majority of respondents represented National Health Service (NHS) clinical pathology departments (85%, 34/40), with the remaining 15% (6/40) of responses from university academic pathology units. Of the 34 clinical pathology departments that responded, 10 were based in district general hospitals, and 24 in tertiary referral centres.

Type of institution	% of responses	No. of responses
NHS - tertiary referral centre	60.0	24
NHS- district general hospital	25.0	10
University academic department	15.0	6
Total		**40**

Table 1. Respondent department characteristics

The clinical departments surveyed varied greatly in size, with the number of whole time equivalent consultants ranging from 4 to 47, and the estimated number of histopathology cases accessioned per year ranging from 2000 to 90000.

2.4.2 Access to and ownership of digital pathology hardware

60.0% (23/39) of participating institutions had access to a digital pathology scanner. Of these institutions, 34.8% (8/23) had an NHS-owned scanner, 43.5% (10/23) had a university-owned scanner and 21.7% (5/23) had access to a scanner owned by neither the NHS nor the university (see figure 5).

60.0% (24/40) of institutions had access to a digital pathology workstation, but only 46.2% (18/39) had access to a digital slide archive or library.

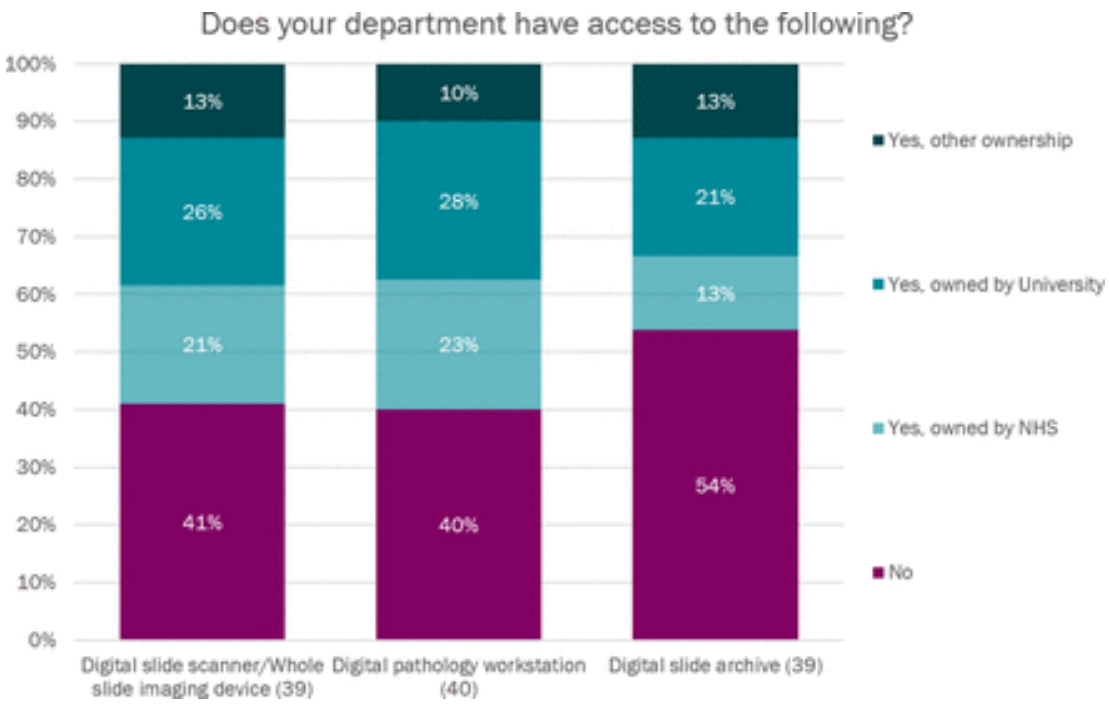

Figure 5. Access to and ownership of digital pathology hardware. Availability of NHS and non NHS owned digital slide scanners, workstations and archives.

2.4.3 Current digital slide usage

58.8% (20/34) institutions reported that they do not currently produce any digital slides. Of the institutions that currently produce scanned slides, the annual total ranged from 50 slides to 30 000 slides.

The most popular applications of digital pathology in current use were undergraduate and postgraduate teaching, research and quality assurance.

Experience with direct clinical use of digital pathology was less widespread, but 31% of departments indicated they use digital slides for primary diagnosis and 36% for secondary diagnosis, in a proportion of cases (see figure 6).

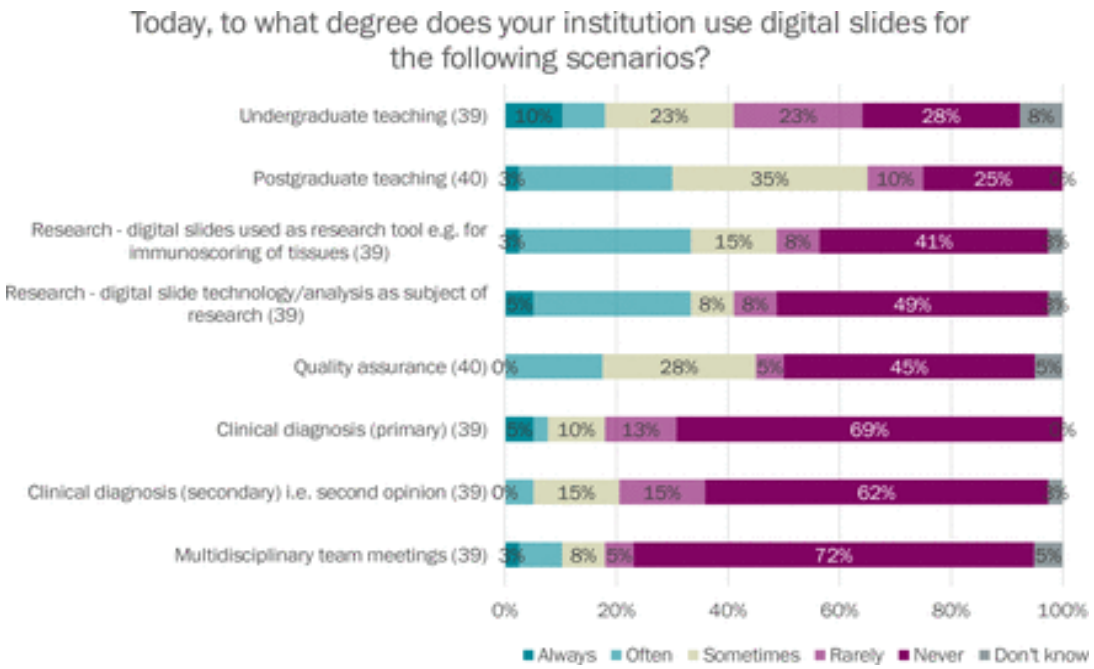

Figure 6 Current usage of digital slides. Digital slides are used for a variety of purposes, ranging from education and research to primary diagnosis.

2.4.4 Predicted digital slide usage

When asked to predict their institution's projected usage of digital pathology in 1 year's time, an increased proportion of institutions predicted that digital slides would be used always or often for all digital slide use types (see figure 7).

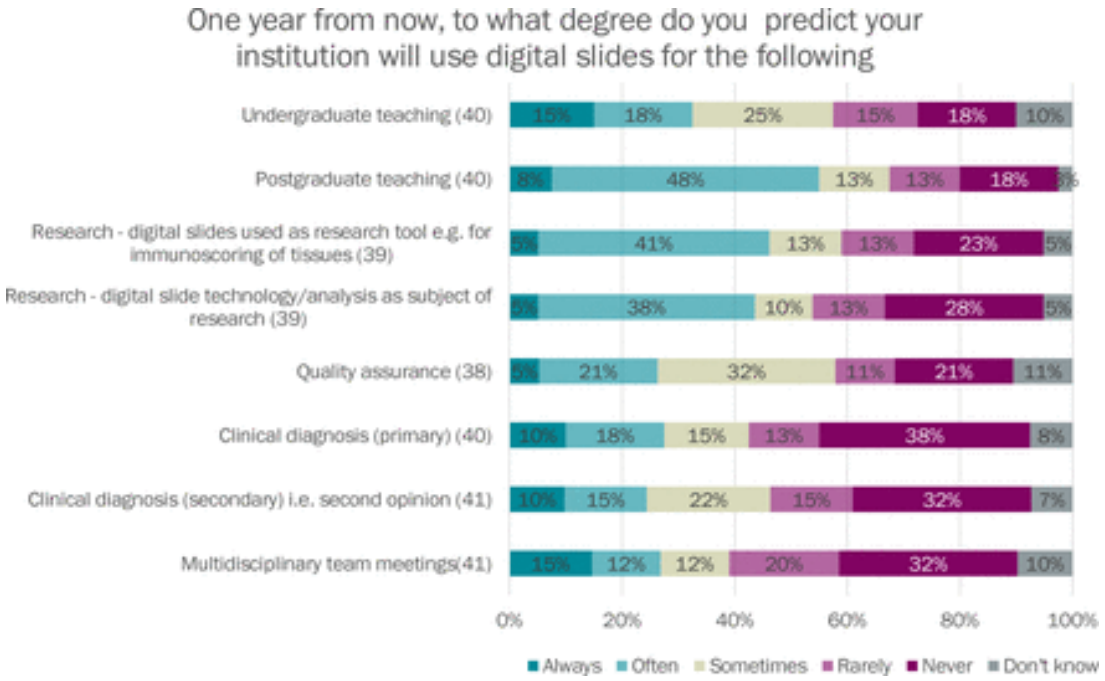

Figure 7 Projected usage of digital slides. Departmental predictions of usage in one year's time.

2.4.5 Image analysis usage

41.0% of institutions (16/39) report that they currently use image analysis on digital slides, with immunoscoring, tumour environment assessment, basic measurements, tumour cell proportions and tumour segmentation given as examples of current usage.

2.4.6 Attitudes to digital pathology adoption and usage

The majority of departments (24/41, 58.5%) listed the investigation and use of digital pathology as a high or essential priority at their institution (see table 2).

Digital pathology prioritisation	% of responses	Number of responses
Not a priority	9.8	4
Low priority	14.6	6
Neutral	17.1	7
High priority	43.9	18
Essential priority	14.6	6
Total		**41**

Table 2 Prioritisation of digital pathology for institutions

When asked about the perceived benefits of digital pathology for their department, the majority of respondents agreed or strongly agreed that digital pathology would improve efficiency, turnaround times, reporting times and collaboration in their institution (figure 8). Overall laboratory costs and safety were the only parameters that the majority of respondents did not think would be improved by introducing digital pathology.

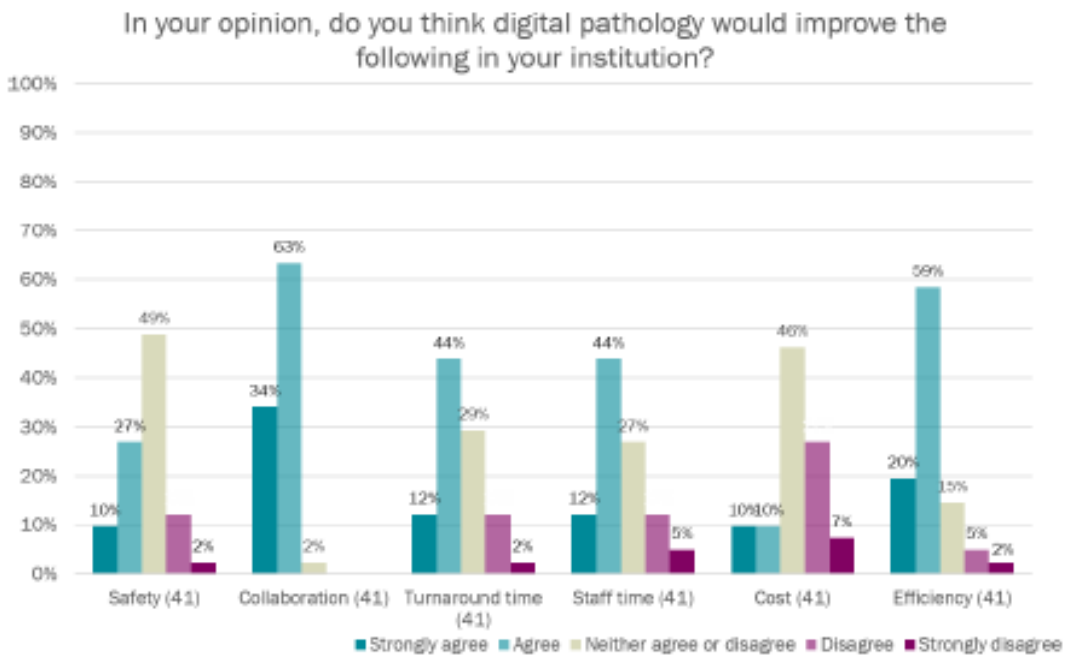

Figure 8 Perceived benefits of digital pathology. The potential benefits of digital pathology, as viewed by participating institutions.

2.4.8 Perceived barriers to digital pathology adoption

Respondents were next asked what they perceive to be the barriers to wider digital pathology adoption. 82.5% of respondents agreed or strongly agreed that initial financial cost was a barrier to wider digital pathology usage at their institution, while only 15% agreed that safety concerns were impeding more widespread use of digital slides (see figure 9).

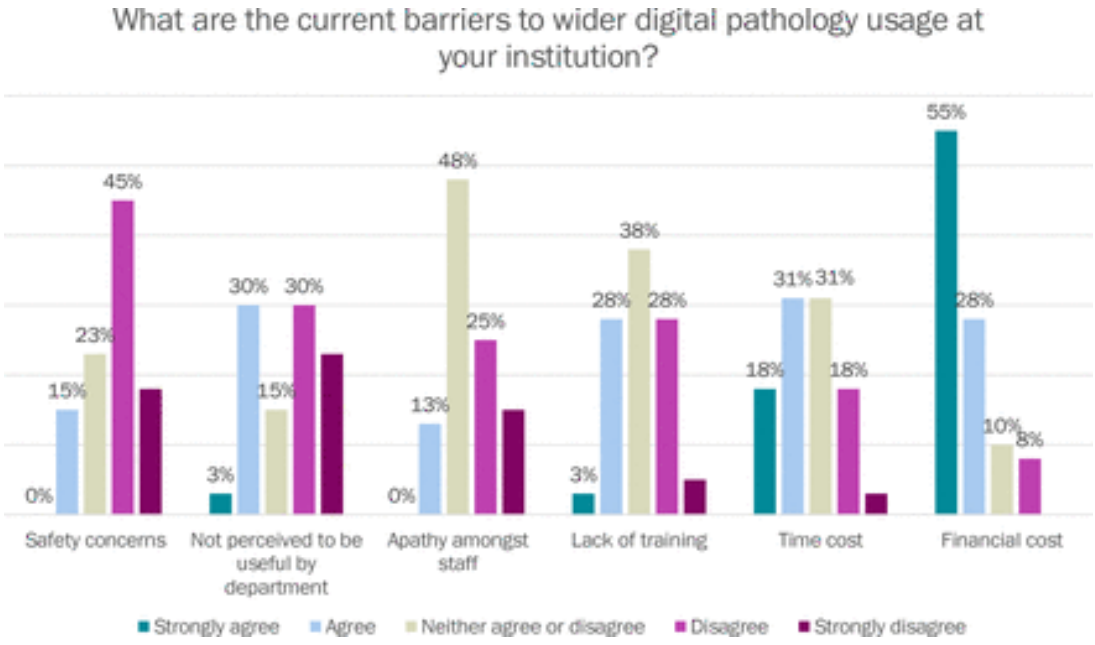

Figure 9 Perceived barriers to digital pathology. The barriers to digital pathology, as reported by the participant institutions.

2.4.9 Factors facilitating digital pathology usage

Access to funding for initial hardware, software and staff outlay, training for pathologists and guidance from the Royal College of Pathologists were identified as factors that could enable respondent institutions to increase their digital pathology usage (see figure 10).

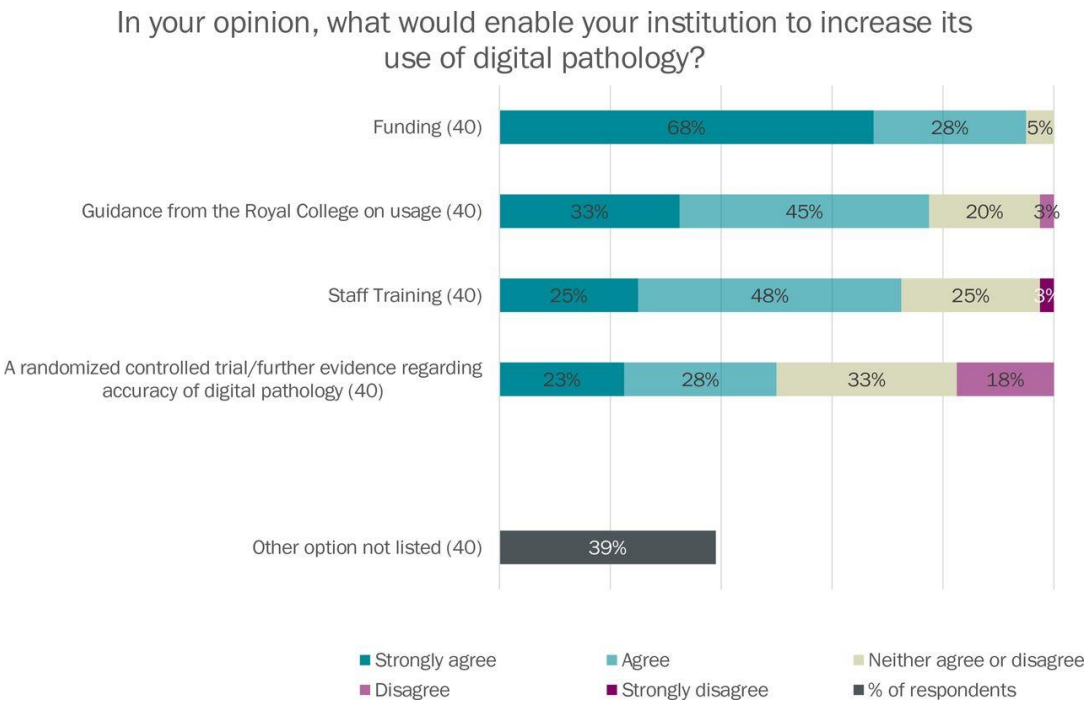

Figure 10. Factors that could enable digital pathology usage. Key factors enabling digital pathology, as indicated by participating institutions.

The following additional enabling factors were identified by respondents, and included as free text:

- Relevant UK data proving cost savings.
- Public Health England (PHE) approval for screening specimens.
- NHS England taking a clear and strong stance on digital pathology.
- Improved internet connections.
- Algorithms which improve reporting standards.
- A change in attitude from managers.
- Information technology infrastructure and personnel support.

2.5 Discussion

This NCRI's CM-Path survey was the first attempt to gather national data on access to and usage of digital pathology in NHS and academic pathology departments in the

UK. Sixty per cent of respondents had access to WSI scanners, with ownership of these devices split between the NHS and linked university departments. 41.2% of institutions reported that they currently actively produce digital slides in their department, with the most popular applications being for education, research and quality assurance purposes. Interestingly, 31% of respondents indicated that they currently use digital slides for primary diagnosis in a proportion of cases, and 36% use digital slides for secondary diagnosis, indicating that pathology departments are finding utility for the use of digital slides in certain aspects of clinical practice. Predictions for slide usage 1 year from now suggest more departments will be using digital pathology for diagnostic work, and for a greater proportion of cases in the near future.

One of the most interesting findings of the survey was reported level of prioritisation for digital pathology adoption or investigation in the respondent institutions, with the majority of respondents listing it as a high or essential priority. Participants were optimistic that digital pathology could help improve diagnostic efficiency and turnaround time, and 97.6% agreed or strongly agreed that digital pathology could improve collaboration in their department. Interestingly, patient safety aspects of digital reporting were not emphasised by the survey respondents, despite the potential to reduce patient misidentification errors by creating a paper-light or paper-free workflow.

The most prevalent existing barrier to wider digital adoption for the survey respondents was financial cost to their department. There have been long economic arguments in favour of the introduction of digital pathology in many contexts, but

there is undoubtedly significant initial outlay, in terms of hardware and software, and ongoing training, maintenance and personnel costs. The time required to set up and deploy a system, train staff and ongoing staff time costs to run scanners was also implicated as a barrier for some departments. Clearly, these barriers would need to be counterbalanced by the potential major benefits for diagnostic workflow, workload and workforce issues, and service quality and safety. Little concern was expressed regarding the safety and accuracy of digital pathology diagnosis versus conventional slide diagnosis, which may reflect the evolving evidence base for digital and glass slide diagnostic concordance. A recent systematic review, published by a group including myself[38] found a glass:digital concordance rate of 92.4%.

92.5% of respondents agreed or strongly agreed that funding was required to aid increased uptake of digital pathology in their institution, and 78% wanted guidance from the Royal College on digital pathology usage. Interestingly, more people identified Royal College guidance as a digital pathology enabler than a randomised controlled trial of digital pathology accuracy, and this may help more departments evaluate the opportunities and risks of digital pathology adoption in their department. In free-text statements, respondents also indicated that a need for direction from NHS England and an approval from Public Health England (PHE) were needed to enable them to move forward with digital pathology adoption.

The results of the survey suggest that interest in digital pathology adoption in the UK is high, and that an increasing proportion of pathological diagnosis will be made on digital slides in the immediate future. Furthermore, the recently published Life Sciences Industrial Strategy recognises the need for increased adoption of digital

pathology within the NHS,[19]citing that digital pathology will allow the use of artificial intelligence that could provide prognostic insights that are currently unavailable. To support this adoption, pathology departments would value clear guidelines and statements from key national healthcare, professional and regulatory bodies regarding their position on digital pathology in the clinic, and the necessary steps to take to ensure any adoption maintains or improves on current standards of quality and safety.

With this in mind, in chapter 3 the evidence base for the diagnostic accuracy for digital pathology is analysed, with the aim of identifying key safety and educational points which could inform the design of a digital pathology training and validation protocol.

Chapter 3. Evaluating the evidence for the safety of primary digital diagnosis

This chapter summarises work by the author from the following publication:

Williams BJ, DaCosta P, Goacher E, Treanor D.

A Systematic Analysis of Discordant Diagnoses in Digital Pathology Compared with Light Microscopy

Archives of Pathology and Laboratory Medicine 2017:141:1712-1718

3.1 Introduction

The review of the literature outlined in chapter 1, and the results of the national survey described in chapter 2 suggested that pathologists were seeking support and advice with education and training in digital pathology.

Clinical adoption of digital pathology at scale requires more than the approval of regulatory bodies and departmental heads and decision makers. It requires that individual pathologists can be confident that a diagnosis they make on the digital microscope is equivalent to a diagnosis they make on the conventional light microscope. Achieving this level of confidence is likely to be a different journey for different individuals, but a core part of this is feeling that personal educational and professional development needs have been met.

3.1.1 Systematic Review of the concordance of WSI and light microscopy

A limited number of studies have compared the diagnostic concordance of WSI and traditional light microscopy. In 2016, the author was part of a team that undertook a

systematic review of diagnostic accuracy studies of WSI, in which the quality of studies was explored .[38] Thirty-eight qualifying studies were identified, consisting of 6 crossover studies (16%), 19 prospective comparative reviews (50%), and 13 retrospective retrieval and review studies (34%). The mean number of cases within the included studies was 140. Sixteen studies (42%) used participants trained in using WSI systems. Washout periods between comparisons ranged from none to more than 12 months. Eight WSI scanner manufacturers were represented in the studies, with Aperio (Aperio, Vista, California) scanners used in the majority of the studies (n = 23; 61%). Interobserver agreement was measured in 6 studies (16%), whereas 32 studies (84%) measured intraobserver agreement. The most commonly studied individual organ system was the gastrointestinal system (n=7; 18%). Ten studies (26%) were a mix of 2 or more distinct organ systems.

The study reported a mean diagnostic concordance of WSI and light microscopy, weighted by the number of cases per study, of 92.4%. Of the 30 studies quoting concordance as a percentage, 60% showed a concordance of 90% or greater, of which 10 showed a concordance of 95% or greater. There was a trend for increasing concordance in the more recent studies. Concordance levels were higher in studies which explicitly documented that participant pathologists had been trained in the use of the WSI system. The review found evidence to support a high level of diagnostic concordance for WSI overall.

3.1.2 A systematic analysis of discordant digital diagnosis

The conclusions of the systematic review can be interpreted as encouraging for a diagnostic department that is considering a primary diagnostic digital adoption;

however, if one inverts the statistic, 92.4% concordance equates to 7.6% discordance. It can be argued that discordances are more valuable than concordances in analysing the potential patient safety impact of digital diagnosis, and an evaluation of the type, severity, unexpectedness, and root cause of these discordant diagnoses can allow us to explore safety aspects of digital pathology adoption and identify potential pitfalls—areas of digital diagnostic interpretation that may require more attention or practice before full digital adoption for primary diagnosis. Experience in analysing error rates and types in telepathology, including that published by Dunn et al,[48] has contributed greatly to our understanding of the limitations and strengths of this diagnostic medium, and gathering and analysing similar data from WSI studies is likely to prove equally beneficial.

The primary aim of this review and analysis was to systematically examine the published literature on discordant pathologic diagnoses rendered by WSI compared with those rendered by light microscopy, and to identify areas that may be problematic to diagnose using digital microscopy.

3.2 Materials and methods

A systematic review protocol that had been used in our previous systematic review of WSI concordance was used.[38] The review protocol is registered with the PROSPERO database (registration number CRD42015017859).

3.2.1 Search Strategy

An electronic search was instigated on the databases Medline, Medline in Progress, EMBASE, and the Cochrane Library between 1999 and December 2015, using the

previously published systematic review methodology. [38] A search of clinicaltrials.gov (Bethesda, Maryland) was performed to identify any ongoing studies. Included studies underwent manual reference searching and citation tracking through PubMed and Google Scholar. Corresponding authors were contacted, where possible, to identify subsequent or ongoing research.

3.2.2 Paper Screening

Two pathologist reviewers independently subjected the abstracts of papers to the previously used systematic review screening algorithm.[38] In cases of disagreement, a third independent pathologist reviewer was consulted. Full texts of all papers that fulfilled the initial screening algorithm were retrieved and reviewed. Only published journal articles were included in the review.

3.2.3 Data Extraction and Analysis

A standardised data extraction protocol was applied to all included studies. Pairs of discordant diagnoses were extracted (preferred diagnosis with discordant diagnosis) and were stored in a spreadsheet in which the source study and the method of diagnosis (glass or digital) used to render each diagnosis were concealed from the reviewers. A team of 3 discordance reviewers was assembled, all of whom were professional diagnostic pathologists, with 6, 18, and 34 years of pathology experience.

The 3 discordance reviewers evaluated each diagnostic pair and assigned it a category based on the Royal College of Pathologists System of Categorisation for Discrepancies.[49] In this system, discordances are assigned a letter code depending on

the type of error (ie, errors in macroscopy, microscopy, clinical correlation, failing to seek a second opinion, misidentification). For this study, the B category, discrepancies in microscopy, was the most relevant. The B category errors are then stratified depending on how unexpected or understandable the error is (Table 3).

Category	Description
A	Inadequate dissection, sampling or macroscopic description
B1	Discrepancy in microscopy – a diagnosis that one is surprised to see from any pathologist
B2	Discrepancy in microscopy – a diagnosis that is clearly incorrect, but that one is not surprised to see a small percentage of pathologists suggesting
B3	Discrepancy in microscopy – a diagnosis where interobserver variation known to be large (eg. difficult diagnosis, difference between 2 tumour grades)
C	Discrepancy in clinical correlation
D	Failure to seek a second opinion in an obviously difficult case
E	Discrepancy in report (includes misidentification)

Table 3. Summary of Royal College of Pathologists system of categorisation for discrepancies. Each discrepancy is assigned an alphanumeric code indicating the type of error.

Next, each reviewer assigned each discordant diagnostic pair a category corresponding to the potential for patient harm to be caused, from the Royal College of Pathologists guide to duty of care reviews (Table 4).[50] The spectrum of harm ranges from no clinical impact, no harm, which is categorised as 1, to severe harm, categorized as 5. Dimensions such as delay in diagnosis, unnecessary further

diagnostic efforts, delays in therapy, unnecessary therapy, and resultant levels of morbidity or mortality were considered. All discordances were reviewed independently by the 3 discordance reviewers.

Category	Description
1	No impact on care.
2	Minimal harm, no morbidity. Delay in diagnosis or therapy only, of less than 3 months. Unnecessary noninvasive further diagnostic efforts. Unnecessary therapy without morbidity.
3	Minor harm, minor morbidity. Delay in diagnosis or therapy only, of more than 3 months. Unnecessary invasive further diagnostic efforts. Delay in therapy with minor morbidity.
4	Moderate harm, moderate morbidity. Due to delay in diagnosis, due to otherwise unnecessary diagnostic efforts, due to otherwise unnecessary therapeutic efforts.
5	Major harm, major morbidity. Loss of limb, organ, or function of organ system due to unnecessary therapeutic efforts. Death.

Table 4. Summary of Royal College of Pathologists categorisation of discrepancies for duty of care reviews. Each discrepancy is assigned a category number indicating the potential for harm to be caused to a patient.

For the potential for harm categorisations, the Royal College categories 2 and 3 (minimal harm, no morbidity, and minor harm, minor morbidity) were merged into a single category of minimal/minor harm, and categories 4 and 5 (moderate harm, moderate morbidity, and major harm, major morbidity) were merged into a single category of moderate/major harm. Where reviewers disagreed on the categorisation of a diagnostic discordance, cases were discussed and a consensus reached. Expert opinion was sought on the renal transplant biopsy data, as the review team did not

feel they had sufficient subspecialty expertise in this area (Dr Carole Angel, MB, ChB, Leeds Teaching Hospitals NHS Trust).

After all cases had been categorized, the lead researcher reunited the discordant pairs with source study data. For each individual discordance, the source paper was examined to extract data determining whether glass or digital slides yielded the gold standard or consensus diagnosis; the type of diagnosis required; the type of discordance; any specific diagnostic tasks, objects, or features that would have enabled the pathologist to make the true diagnosis; and detail from the paper of any particular difficulties/observations encountered by the study pathologists. See Table 5 for an example of a discordance analysis.

Parameter	Example
True diagnosis	Focal active colitis
Discordant diagnosis	Normal colon
Gold standard diagnostic modality	Glass
RCPath expression of concern code	B2 (clearly incorrect, but would expect a small proportion of pathologists to make the same error)
RCPath potential for harm code	2 (minor harm, minor morbidity)
Discordance type	Missed diagnosis
Diagnostic tasks/objects/features	Finding and identifying small objects (neutrophils)
Details from paper	Granulocytes difficult to discern on digital. Improved at 40x.

Table 5. Example of a discordance analysis for a colonic biopsy. In this case, the gold standard, "true" diagnosis was made on the glass slide, and a discrepant diagnosis was made on the digital slide.

3.3 Results

3.3.1 Study Demographics

One thousand three hundred abstracts were checked and 39 full-text papers extracted. Of these, 23 contained detailed, extractable discordant diagnostic pair data.[51-73] Publication dates ranged from 2006 through 2015, with the majority of studies published post-2010. These 23 papers included 8069 instances of a glass diagnosis and a digital diagnosis being compared. Out of these 8069 glass-digital read pairs, 335 instances of discordance were recorded, which represents approximately 4% of 8069 glass-digital comparisons. The included studies used a range of scanners from 7 different vendors. Viewing hardware varied greatly both within and among studies. Many studies provided little information on viewing hardware/scanners or failed to standardise viewing hardware. The majority of studies scanned slides at a routine magnification of 20x, with more recent publications tending to use 40x, and some varying the scanning magnification depending on the type of case, for example, diagnostic specimens at 40x and therapeutic specimens at 20x.

The majority of included studies scanned a mixture of cases from a number of histopathology subspecialties. Ten studies were a mix of 2 or more distinct organ systems, which was termed a case mix, with gastrointestinal and skin the most popular single pathology specialties examined. The majority of recorded discordances occurred in gastrointestinal, skin, genitourinary, and gynaecological cases. Unfortunately, many of the source studies lacked a sufficiently detailed breakdown of case types included, but it is likely that cases from these organ systems

are overrepresented in the source studies. They are certainly all high-throughput specialties.

3.3.2 Severity and Implications of Discordance

Of the 335 reported discordances, glass was the preferred diagnostic modality in 286 cases (85%). Interestingly, the digital diagnosis was preferred in 44 cases (13%), with an equivocal response in the remaining 6 (2%). The largest specific category of discordance was missed diagnosis of malignant/dysplastic/atypical conditions, where malignant tissue was given a benign diagnosis. In these cases, glass was the preferred diagnostic modality in 66 of 77 cases (86%). There were also 25 cases where benign tissue was erroneously diagnosed as malignant/atypical. Here glass was the preferred diagnostic modality in 23 cases (92%) (Table 6).

The second greatest discordance type (70 cases) was where a case was recognised as malignant/atypical but incorrectly typed or graded. Here again, glass was the preferred diagnostic modality in 67 cases (96%). Discrepancies in the diagnosis of inflammation were also common. Most discordances (169 cases) fell into the category of B3, areas of appreciable diagnostic difficulty and recognised interobserver variation, such as the difference between 2 adjacent grades of a malignant condition. In total 21 B1 diagnoses were recorded. These would be regarded as surprising errors using the Royal College of Pathologists' System of Categorisation for Discrepancies.[49] One type E discordance was recorded—a misidentification error, where digital was the preferred diagnostic modality (Table 7).

Discordance type	Glass preferred	Digital preferred	Total
Missed malignant/ atypical diagnosis	66	11	77
Erroneous malignant diagnosis	23	2	25
Difference in malignant diagnosis (including grading/subtype differences)	67	3	70
Missed inflammation	40	2	42
Erroneous diagnosis of inflammation	6	2	8
Difference in diagnosis of inflammation (including subtype/degree)	15	2	17
Invasion missed	2	5	7
Erroneous invasion	4	0	4
Other	63	17	80
Total	**286**	**44**	**330**

Table 6. Types of discordance

Category and description	Glass preferred	Digital preferred	Total
B1 Surprising error	19	2	21
B2 Expect small number of pathologists to make this type of error	123	16	139
B3 Area of appreciable difficulty/interobserver variation	144	25	169
E Misidentification	0	1	1

Table 7. Types of discordance classified by the Royal College system for discrepancy classification.

The majority (242; 72%) of the 335 discordances reported had the potential to cause minimal or minor harm to patients. This represents 3.0% of all glass-digital comparisons (242 of 8069). Only 28 of 335 (8%) had the potential to cause moderate or major harm to patients. This represents 0.35% (28 of 8069) of all glass-digital comparisons. For these, glass was the preferred diagnosis in 26 (93%). Digital was preferred in 2 of 28 cases (7%) with the potential for moderate/major harm (Table 8).

Harm category	**Glass preferred**	**Digital preferred**	**Total**
No impact	51	9	**60**
Minimal/minor harm	209	33	**242**
Moderate/major harm	26	2	**28**

Table 8. Potential for harm in discordant case scenarios.

Table 9 shows specific instances of major/moderate harm recorded on diagnoses made using digital and conventional glass slides. Instances where the glass slide diagnosis was preferred included benign breast tissue erroneously reported as invasive carcinoma on the digital read and a benign lung biopsy erroneously diagnosed as non–small cell carcinoma. Examples where malignant diagnoses were missed on the digital read of a case included gastric adenocarcinoma called acute gastritis, metastatic melanoma missed in a lymph node, and chronic lymphocytic leukaemia missed in a skin biopsy. Digital was the preferred diagnostic modality for 2 cases with the potential for moderate/major harm: a carcinoid tumour that was

missed in the glass examination of an appendix, and benign breast tissue erroneously diagnosed as ductal carcinoma in situ on glass.

Preferred diagnostic modality	Discordant diagnosis	True diagnosis
Glass	Invasive carcinoma with lobular features	Benign breast tissue
Glass	Non-small cell lung cancer	Chronic bronchitis
Glass	Acute gastritis	Adenocarcinoma
Glass	Lymph node, no abnormality detected	Metastatic melanoma
Glass	Dermatitis	Skin infiltration with chronic lymphocytic leukaemia
Digital	Acute appendicitis	Goblet cell carcinoid tumour
Digital	Ductal carcinoma in situ	Fibrocystic change

Table 9. Examples of diagnostic scenarios with the potential to cause major/moderate harm

3.3.3 Types of Discordance

3.3.3.1 Dysplasia Diagnosis

The included studies reported 108 of 335 discordances concerning the diagnosis of dysplasia, representing 32% of all reported discordances. These were predominantly cases from the upper gastrointestinal tract and the cervix. Dysplasia is an area of appreciable interobserver and intraobserver variation, but nonetheless, dysplasia discordances seemed to be particularly prevalent. The majority of discordances were

instances of missed diagnosis, where dysplastic tissue was diagnosed as benign or reactive tissue. Fifty-one cases of this type were reported, and they represented 47% (108) of all dysplasia related discordances. Interestingly, where there were differences in grading, dysplastic lesions tended to be undercalled (undergraded or missed diagnosis as opposed to overgraded or erroneously diagnosed) on the digital microscope (33 cases undercalled, 8 cases overcalled). There were also errors in the other direction, with erroneous dysplasia diagnosed in benign tissue (14 cases) and a smaller number of overcalls in grading (10 cases). Of all the discordant dysplasia diagnoses, glass diagnosis was preferred in 101 of 108 cases (94%). This indicates that diagnosis and grading of dysplasia may be a pitfall of digital diagnosis (Table 10).

Dysplasia discordance type	**Glass preferred**	**Digital preferred**	**Total**
Missed diagnosis	47	4	51
Grading undercall	33	0	33
Erroneous diagnosis	13	1	14
Grading overcall	8	2	10
Total	**101**	**7**	**108**

Table 10. Summary of discordant dysplasia diagnoses

3.3.3.2 Locating Small Diagnostic Objects/Features.

Another common diagnostic feature implicated in discordance is the ability to find or not find a small diagnostic/prognostic object. Thirty-nine discordances of this type were recorded, with glass the preferred diagnostic medium in 30 of 39 (82%). The

majority of these discordances would be classified as B2 errors in microscopy, which one expects to see in a small proportion of cases as a matter of course. Three small object location discordances were classified as surprising errors based on the context. In total, 5 of the small object location discordances could have resulted in moderate/major patient harm. The types of small object missed included a range of malignant and benign features. Perhaps the most concerning of these are small tumors, metastases, and microsatellites. The most common small objects missed were foci of inflammation, more specifically cryptitis in colon biopsies. The detection of microorganisms was also a theme raised in the literature. (Table 11).

Category	**Object**	**Glass preferred**	**Digital preferred**
Neoplasia	Small primary tumour	1	2
	Lymph node metastasis	3	
	Tumour microsatellite	1	
	Focal tumour invasion	3	3
Inflammation	Focus of inflammatory activity	8	
	Granuloma	3	
Micro-organisms	Helicobacter pylori	2	
	Candida	3	
Sparse cells	Reed-Sternberg cells	2	
Focal benign features		5	2
Focal immunopositivity		1	

Table 11. Discordances related to difficulty locating diagnostic objects

3.3.3.3 Specific Problematic Entities Reported in the Literature

Granulocytes were mentioned in 27 of 335 instances of discordance (11%). Disparities in detection of granulocytes, particularly eosinophils, may relate to differences in the colour of the cells on digital and their refractile textures. Similar issues with detection of other eosinophilic, refractile objects (nucleated red blood cells and eosinophilic granular bodies) were reported. Difficulties were also described identifying 2 entities commonly recognised on the grounds of subtle textural and tinctorial qualities: blue mucin and amyloid. In the 2 reported cases of difficulty with amyloid,[73]study participants were unable to detect the textural quality of amyloid on digital slides, which would have alerted them to examine the original glass slides with a polariser (Table 12).

Object/feature	No. of cases
Neutrophils	19
Eosinophils	7
Mast cells	1
Nucleated red blood cells	8
Eosinophilic granular bodies	1
Amyloid	2
Blue mucin	1

Table 12. Objects and features that caused difficulty on digital slide review.

3.3.3.4 Misidentification Errors

There was one confirmed misidentification error, where the reader providing a glass diagnosis viewed the wrong slides, and the digital read rendered the correct diagnosis.

3.4 Discussion

The use of digital pathology in the clinic is increasing, with many departments piloting digital pathology in primary diagnostic settings. In light of this, guidance is needed regarding potential safety implications for patients. A number of validation studies have been reported in the literature, but as the published systematic review indicated,[38] these vary greatly in terms of the number and types of participants and cases, the methodology, and the technologies examined. In the absence of a multicentre clinical trial, a systematic review remains the highest level of digital pathology concordance evidence available for those engaged in regulatory efforts. Goacher et al[38] found a mean diagnostic concordance of WSI and light microscopy, weighted by the number of cases per study, of 92.4%. In this study, the aim was to complement this work with a systematic analysis of the discordant diagnoses reported in the validation literature, in the hope that this analysis would allow a more precise evaluation of primary digital diagnosis.

3.4.1 Dysplasia

The diagnosis and grading of dysplasia is implicated as a possible pitfall of digital diagnosis. Most papers emphasise blurring of nuclear detail on digital scans, and implicate poor focus, exacerbated by compression artefact. These explanations focus on high-power diagnosis, but one should also consider low power. In cervical biopsies, dysplasia is often focal, and if focal abnormality is not picked up on the low-power assessment of the epithelium, confirmatory nuclear detail cannot be

appreciated on high. One may also need to consider the effect of scanning magnification and viewing hardware quality.

What potential strategies do pathologists have to mitigate the risks of diagnosing dysplasia digitally? The first thing that can be done is to ensure pathologists are aware that dysplasia is a potential pitfall. Ordi et al[68] describe an increase in glass-digital concordance for cervical dysplasia as their study progressed, suggesting that there is a significant learning curve effect for digital dysplasia diagnosis. This is an area of diagnosis that may need a longer settling-in period before pathologists can confidently and safely sign out digital cases.

Pathologists working in relevant specialties might want to consider a self-validation procedure, with digital-glass reconciliation of dysplasia diagnoses while they establish satisfactory glass-digital concordance. Alternatively, there might be a role for optional or mandatory checks on glass following a digital assessment in particular scenarios—for example, diagnosing dysplasia in Barrett oesophagus, a practise used in some digital pathology deployments (Anna Boden MD, Linkoping; David Snead, MB, BS, Coventry; verbal communications, January 2016). Some authors describe limited improvement in digital dysplasia diagnosis with slides scanned at 40x, so there may be justification for mandatory scanning of selected specimens at 40x (eg, cervical biopsies, upper gastrointestinal biopsies). Unfortunately, there are insufficient data at present to judge whether scanning at 20x versus 40x has a significant impact on overall discordance rates, and this is an area that deserves more attention in future studies.

3.4.2 Locating Small Diagnostic Objects/Focal Diagnostic Features

Locating small diagnostic objects is highlighted as a potential problem on digital slide reads. Navigation is certainly implicated, both within and among slides, and the effects of display resolution and scanning magnification also warrant consideration. In many studies, authors explicitly state that pathologists found navigating cases cumbersome. Specific training in safe and efficient navigation strategies using digital software should be available to pathologists who are expected to use digital images clinically. Appropriate use of whole slide and whole case thumbnails can aid navigation, and safety features such as indicator lights to warn pathologists of missed slides/regions could help. There may be a case for modifying workflows to incorporate a mandatory glass check, at least in the initial phases of digital deployment, for specimens such as sentinel lymph nodes, where detection of micrometastases should be optimal. There is little evidence in the literature regarding minimum specification for viewing hardware or standardization of viewing hardware. Many authors found diagnostic biopsies, particularly where detection of inflammatory disease is important, were best scanned at 40x, with Snead et al[69] recommending 60x in cases where detection of micro-organisms is a priority.

3.4.3 Specific Objects/Features Causing Diagnostic Difficulty

Examination of the literature highlights a number of specific entities, including granulocytes, nucleated red blood cells, and amyloid, which were reported as having a different appearance on glass and digital slides. The importance or relevance of identifying these entities will vary among different subspecialties, and possibly among different pathologists, but it is important to mention areas where investigators have noticed an appreciable difference in appearance.

Specialty pathologists need to be aware of specialty specific diagnostic pitfalls and decide how important these features are to their own practice. Bauer and Slaw[58] report that scanning gastrointestinal biopsies at 40x improved the ability of their pathologists to detect and correctly categorize granulocytes. Colour calibration may potentially play a role.

3.4.4 Misidentification Errors

A single case of misidentification error was reported in the review source literature. In this case, the correct diagnosis was rendered on the digital slide, and the glass slide reviewer viewed the incorrect glass slide. It perhaps reminds us of the potential digital technology provides us to avoid the type of pathology error that should never occur: the misidentification of specimen, slides, or reports. The types of study design used in the source material for this analysis are unlikely to expose the full extent of misidentification errors, which should be considered when evaluating the total impact of digital versus glass technology on diagnostic error rates.

3.5 Conclusions

Given the increasing trend towards using digital pathology for clinical diagnosis, including primary diagnosis, the need for evidence-based digital pathology guidelines and a systematic evaluation of the available evidence is paramount. In this analysis of 8069 comparisons of glass and digital diagnoses, 335 discordances were found. Of these, only 28 had the potential to cause moderate or major patient harm.

A number of problem areas in digital diagnosis were found that warrant further exploration and explanation; namely the identification and grading of dysplasia, the

location of small diagnostic objects and features, and the identification of certain specialty-specific diagnostic features. This information can be used to inform safe departmental or institutional adoption of digital pathology and to help design systems and process to address these areas in the future. Although digital deployment for primary clinical diagnosis is in its infancy, it is important to collect and share data on pitfalls and problem cases. To this end, it might be helpful to create a centralised database of problematic cases, recorded in a standardised format.

Education and continuing professional development of pathologists on an individual level is vital to ensure a safe and responsible rollout of digital microscopy. Pathologists should be encouraged to gain confidence in risk-free or risk mitigated diagnostic environments before adopting a 100% digital workflow. The perceived success or failure of digital pathology in a specific laboratory will stand or fall based on the competency and confidence of individual pathologists, and it is therefore important that pathologists understand the strengths and limitations of the WSI systems. The studies included in this analysis used a wide variety of different scanners, with different characteristics that could affect diagnostic interpretation of slides. In light of this, it can be argued that it is important that diagnostic departments perform their own whole-system validations for WSI, to evaluate the strengths and weaknesses of the combination of hardware and software components they propose to use for primary diagnosis.

Chapter 4. Developing a training and validation protocol for primary histopathological diagnosis using digital pathology

4.1 Background

For digital pathology to be accepted by the clinical pathology community for standard reporting practice, pathologists will need to feel confident in their abilities to diagnose using digital slides. From the author's experience working with the Leeds pathology cohort, and visiting other facilities in the UK and Europe, departments generally have an even mix of 3 types of pathologist when it comes to digital adoption: "enthusiasts", "uncertains" and "sceptics". The enthusiasts are the typical early adopters, who embrace technology with enthusiasm and positivity – they are eager to deploy and use digital pathology as soon as possible. At the other end of the spectrum are the sceptics, who are quick to identify potential problems with digitisation and its impact on their working day, service delivery and the profession. Members of both groups are usually vocal in their opinions, and can exert influence over the third group, the "uncertains".

These are individuals that tend to resist any attempts to engage them in discussions or planning meetings regarding digital pathology. Their worries and concerns are harder to elicit. A comprehensive departmental training programme for digital pathology should provide a useful and meaningful experience for members of all three groups, not just the enthusiasts, and equip them with skills and approach to report digital cases safely and confidently.

4.2 General principles and overview

Digital pathology remains a relatively novel technology, and while the literature suggests it is safe, there is limited experience of its use in clinical practice. In light of this, a cautious, safety focused approach, where microscopes are still readily available for slide review where needed would seem prudent.

Any histopathology department will usually house a mixture of enthusiasts and sceptics, and pathologists are a heterogeneous population in terms of their background computer skills, attitude to technology and attitude to risk. A pathologist needs to reach a state where they are not just competent, but confident in their use of the digital pathology reporting system and the validity of their digital diagnosis. A number of approaches are possible, but a successful training and validation procedure should result in:

- Pathologists that are confident in their abilities and their limitations with digital diagnosis.
- Pathologists that are familiar with their hardware and software and can recognise and report performance issues.
- A department with a shared understanding of and investment in their digital pathology system.
- A department that can develop bespoke ways of using digital to improve its outputs, workflows and working environment.

The College of American Pathologists validation guidelines advises that a minimum of 60 cases per “use case” should be viewed on digital and glass, with a washout period of at least 2 weeks between reads and diagnostic concordance rate observed.[74] This experimental validation design can help a department confirm that

their digital pathology system produces diagnostic grade images, but does not offer the individual pathologist an opportunity to gain competence and confidence in digital reporting. The Royal College of Pathologists recommends training and validation which reflects 'real world' diagnosis, with the emphasis on individual professional development.[1] The validation protocol developed at Leeds Teaching Hospitals NHS Trust combines a brief period of hardware and software familiarisation, followed by focused training using cases relevant to the pathologists workload which test potential 'pitfalls' of digital diagnosis and a period of dual reporting, with initial digital assessment followed by a safety check on glass slides.

Pathologists can train singly or in small cohorts, ideally grouped by subspecialty. Ideally, a departmental 'trainer' should oversee the validation of colleagues. This could be a consultant or suitably enthusiastic trainee. Alternatively, pathologists could self-train and self-validate, although discussion with peers is recommended where possible, as this facilitates sharing of and access to a wider range of 'difficult cases' and early discussion of departmental workflows.

Validation stage	Overview
Training (T)	One to one formalised training in digital microscope use Observed practice with feedback
Validation – training cases (V1)	Training set of approximately 20 challenging and informative cases relevant to the individual pathologists regular workload. Participant views the cases as WSI, makes notes on diagnosis and diagnostic confidence in a workbook, then immediately checks the glass slides of the case, and records any change in their assessment of the case. Allows identification and mitigation of pitfalls.
Validation – live reporting (V2)	All cases scanned prospectively. Diagnosis made on WSI, with reconciliation with glass slides before case sign out. Pathologist aims to complete approximately 2 months whole time equivalent workload. Difficulties reported and discussed. Library of problematic cases assembled and reviewed.
Summary and recommendations (S)	Validation document produced for individual pathologist documenting concordance and diagnostic confidence throughout the validation. Recommendation made for scope of digital reporting practice or further training.

Table 13. Summary of the validation and training protocol for primary digital diagnosis.

4.3 The protocol phases in detail

4.3.1 Training phase

The aim of the training phase is to allow the pathologist to familiarise themselves with the hardware and software components of their departmental digital pathology system and provide feedback on the pathologist's use of that system to optimise their initial experience of digital reporting. An initial training package could include a group or individual teaching session based on a powerpoint presentation. This presentation should include the following:

- Description of the components of the departmental digital pathology system (scanners, image management software, reporting workstations including diagnostic screens, slide viewing software).-
- Stepwise description of the validation/training protocol (outlined in table 1).
- Description of digital pathology workflows in the laboratory.
- Description and examples of common digital image artefacts/ system performance issues and how to report these to appropriate team members.
- Commonly encountered areas of diagnostic difficulty on digital slides (these will be discussed later in this thesis).
- Contact details of key team members who can answer queries regarding digital pathology training, validation, scanning and so on.

At this stage, pathologists can be given access to a digital copy of the training presentation, standard operating procedures (SOPs) for digital pathology validation, an SOP for digital reporting and a guide/instruction manual to using the digital pathology slide viewer. After this, it is useful to have an individual session with the pathologist, in which trainer and pathologist open and view training cases. These

should include larger, multislide cases which require navigation between slides. The trainer can observe the pathologist's use of the mouse/other input device and offer suggestions for ergonomic and efficient navigation of slides and specimens. Basic features of the viewing software, including use of zoom and measurement and annotation tools should be demonstrated, until the pathologist is happy to open, navigate and assess cases without the assistance of the trainer.

4.3.2 .Validation training cases (V1)

In this part of the validation, the pathologist views a set of pre-prepared educational cases, which are selected to reflect areas of expected diagnostic difficulty on digital and represent learning targets. The slide sets should be assembled from local departmental archives, so they represent the histology and staining protocols from the participant's own laboratory/laboratories. Case sets should be assembled which reflect the practice of the individual pathologist – for instance, a breast pathologist should just view breast cases, someone that reports that lung and skin should view a mixture of both topographies. Care should be taken to include a range of tissue types, diagnoses and stains. It may be helpful to recruit a trainee pathologist to help assemble cases and create topographical training sets— these are also a fantastic resource for trainees to view. A maximum of 20 cases would seem prudent to balance training needs and time constraints of pathologists. 'Cases' can be a mixture of complete, multislide cases and single representative slides of particular entities. Inclusion of complete resection cases allows the pathologist to test their digital slide navigation skills and competence in use of digital measuring tools, while single slide cases can be used to demonstrate the digital appearance of particular diagnostic

features (eg, amyloid, weddelite) and to assess their skills in digital dysplasia grading and mitotic scoring.

Once collected, the glass slides for the training cases should be scanned using the departmental scanning protocol. At Leeds, scanning at 40× equivalent magnification is recommended for primary diagnostic work. The pathologist should be given access to the digital slides for the cases and the relevant clinical information pertaining to the case. The pathologist should view the digital slides for a case, record their diagnosis in a workbook and record their confidence in that diagnosis on a Likert scale of 1–7. They should then immediately consult the corresponding glass slides of the case and directly compare the glass slide and digital slide representation. This form of validation by direct comparison allows the pathologist to appreciate subtle differences in the representation of the case on digital and glass slides and become confident in their interpretation of the digital slide. The pathologist should record any change in their assessment of the case after consulting the glass and again record their diagnostic confidence. Once the pathologists have viewed all the cases, they can discuss these with the trainer and their colleagues and will hopefully have identified some key areas to concentrate on as they move on to the live reporting phase of the validation.

4.3.3 Validation—live reporting phase (V2)

In this phase of the validation, the pathologist is asked to make all their live diagnoses on digital slides, using their own workload. The pathologists make their diagnosis on the digital slides, but with immediate glass reconciliation prior to case sign-out. A whole time equivalent of 2 months allows the pathologist to view an appropriate

breadth and depth of cases, including an appropriate mix of biopsies and resections. The length of time needed to gain confidence in digital reporting is likely to vary by pathologist, and some may take longer to navigate the learning curve than others. The pathologist should record all cases viewed and record any alterations made to diagnoses following glass slide review on a spreadsheet. The pathologist should be given regular opportunities to discuss discordant or difficult cases with the trainer/their peer group. Discordant cases should be collected and used to create a library of 'difficult on digital' training cases, which can be used as a departmental resource for further training.

4.3.4 Validation summary and recommendations (S)

When the pathologists have completed a suitable period of live reporting, their spreadsheet data should be reviewed and concordance and discordance statistics calculated and put into a report. Data reports should include:

- Record of all training meetings.
- Training set concordance rate as a %.
- Detailed description of discordances from the training set.
- Total number of cases viewed in the live reporting phase.
- Number and percentage of concordant cases.
- Detailed description of discordances from the live reporting phase.

Following review of the data, the pathologist and trainer should reach a mutual decision on the result of the validation procedure. There are three possible outcomes:

1. Fully validated for primary digital diagnosis in the specified diagnostic area.

2. Validated for primary digital diagnosis in the specified diagnostic area, with some exceptions.

3. Not validated for primary digital diagnosis in the specified diagnostic area at this time.

In the majority of cases, an outcome '2' will be the most appropriate designation. In this case, the pathologist and trainer should agree on the scope of digital practice and mandate glass slide checks for particular diagnostic scenarios/case types outside of the scope. For instance, if at the end of the validation procedure, the pathologists still lack confidence in mitotic scoring, they could agree to safety net glass slide reconciliation before sign-out for cases with borderline/critical mitotic count scores. As the pathologist gains experience post-validation, the scope and exceptions can be reviewed and modified as appropriate.

4.4 Conclusion

The validation protocol was developed with the needs of all 3 categories of pathologist in mind: the enthusiasts, uncertains and sceptics. (See figure 11).

The enthusiasts get to experience real-world digital reporting as soon as they have completed their brief training set in V1. The period of glass slide checking in V2 allows some time for reflection and appreciation of difficulties they may not have anticipated. The "uncertain" pathologists get the assurance of a safety net – they can explore the technology and its capabilities in a risk modified setting, without committing to full digitisation. The more sceptical members of a department get to put the clinical WSI system through its paces, and will be able to provide focussed

feedback on parts of the system and workflow that succeed, and those that are in need of modification.

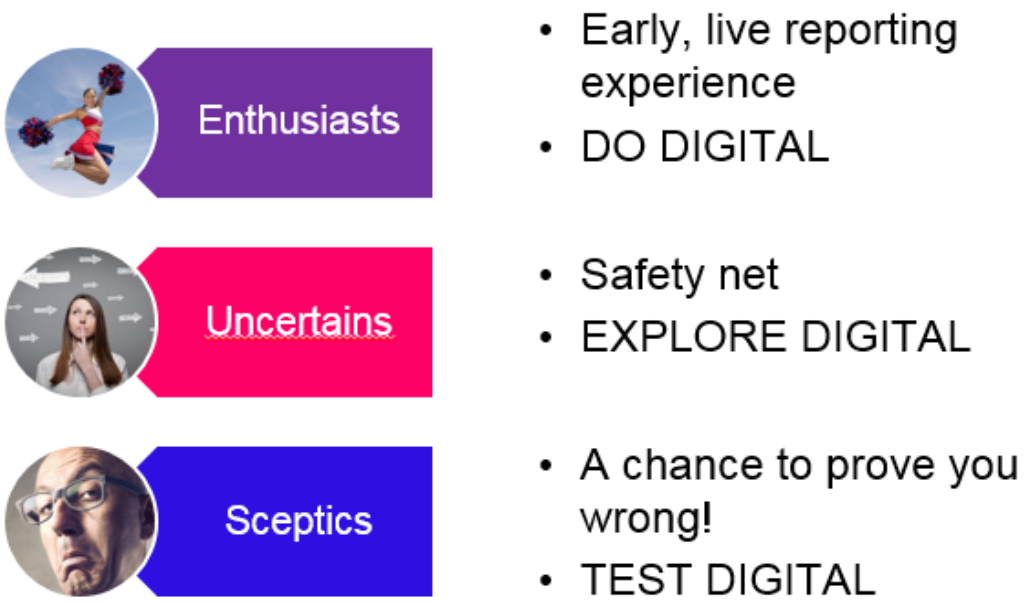

Figure 11. Categorisation of pathologists. Experience at Leeds Teaching Hospitals suggests that pathologists can be divided into 3 categories: the enthusiasts, the uncertains and the sceptics.

Following development of the protocol, the decision was made to trial it on a cohort of 3 specialist breast histopathologists. This group was chosen for a number of reasons. Firstly, breast pathology is an area with appreciable inter- and intraobserver variation, where diagnosis is often dependent on tasks that my systematic analysis (chapter 3) suggested might be difficult on digital slides (eg. nuclear dysplasia, mitotic counts, weddelite detection. Secondly, for historical reasons, the breast pathologists are located in a separate wing of the hospital at St James' University Hospital from the histology laboratory and the rest of the diagnostic pathologists. Reporting of glass

slides was dependent on infrequent, often unpredictable delivery of glass slides by a porter from the laboratory, to this separate wing. WSI reporting could offer early benefits to this group, allowing more timely, continuous transfer of slides for reporting. Finally, and fortuitously, a pre validation questionnaire distributed to the group suggested that the three pathologists represented all 3 categorisations – enthusiast, uncertain and sceptic, and would be a representative group for trial of the protocol. In the next chapter, data from the first instances of real world use of the validation protocol will be presented.

Chapter 5 Validation in practice

This chapter summarises work by the author from the following publications:

Williams BJ, Hanby A, Millican-Slater R, Nijhawan A, Verghese E, Treanor D

Digital Pathology for the Primary Diagnosis of Breast Histopathological Specimens: an Innovative Validation and Concordance Study.

Histopathology **2018;72:662-671.**

Williams BJ, Ismail A, Chakrabarty A, Treanor D

Clinical Digital Neuropathology: Experience and Observations from a Departmental Digital Pathology Training Programme, Validation and Deployment

Journal of Clinical Pathology **2020; doi: 10.1136/jclinpath-2019-206343. [Epub ahead of print]**

In this chapter, the first two instances of clinical use of the digital pathology validation protocol outlined in chapter 4 are described. Firstly, with a cohort of 3 breast histopathologists, and then with a neuropathology team, composed of 2 consultant histopathologists. Both studies were performed in the histopathology department of St James University Hospital, Leeds, United Kingdom, a large academic institution and tertiary cancer centre with full histopathologist subspecialisation, which processes in the region of 250,000 H&E stained histology slides per annum.

5.1 Primary Diagnosis of Breast Histopathology

5.1.1 Background

52000 new breast cancers are diagnosed each year in the UK, accounting for 15% of all new cancer diagnoses, and making this the most common cancer in the UK. [75] Diagnosis of breast cancer, and its differentiation from benign breast diseases is dependent on the histopathological examination of tissue biopsies under the microscope. The use of whole slide imaging in clinical breast pathology is very limited. Digital slides are utilised by medical students and junior doctors in undergraduate and postgraduate medical education, with breast histopathology images accessible online at sites including the online Atlas for Breast Pathology[76] and the virtual microscopy website of the University of Leeds. [77] In research, digital slides allow for simplified centralised review of breast cancer material in large multicentre studies, an option explored by the Prospective Study of Outcomes in Sporadic versus Hereditary breast cancer (POSH) cohort study, amongst many others[78], [79]. In the LORIS trial, which aims to address the overtreatment of screen detected ductal carcinoma in situ, trial entry depends on real time review of digital slides rather than glass slides to assess eligibility. [79]

In clinical pathology breast pathologists are under increasing pressures in terms of breast cancer case volume, case complexity, and the need for rapid evaluation and review to meet cancer diagnostic and therapeutic targets. A small number of digital pathology validation studies have focused on the use of whole slide images for the diagnosis of breast biopsies. Al-Janabi et al demonstrated a 93% concordance rate in a single reader study of 100 breast biopseis[56] whilst Campbell et al found

intraobserver concordance rates between digital and glass diagnosis of 85 breast biopsies for 3 pathologists was 95.4%.[60] Both studies identified discordant diagnoses regarding a select group of diagnostic scenarios: differentiation between hyperplasia and atypical ductal hyperplasia (ADH), the differentiation of benign phyllodes tumours from fibroadenomas, and the identification of foci of microinvasion/lymphovascular invasion. In their validation study, Reyes et al found digital:glass variation in diagnosis varied between 1% and 4% for their 3 pathologists, and in all cases of discordance, the diagnostic issue was the differentiation of ductal hyperplasia from atypical hyperplasia.[80]

The majority of breast digital pathology validation studies in the literature focus on biopsy specimens, whilst in real practice, a large proportion of the pathologist's time is spent viewing resection specimens, where a checklist of histological parameters of an excised tumour need to be assessed and recorded. Shaw et al published their experience reviewing both glass and digital slides of breast cancers from the POSH breast cancer cohort study[78]. 9 pathologists collected data items from digital slides of breast tumours, and then reviewed the glass slides at a later date. Diagnostic performance with the digital slides was comparable to conventional light microscopy. There was better agreement on degree of tubule formation between different reviewers using digital slides than glass slides. The authors suggest that this supports the assertion that the whole slide view provided in digital pathology permits superior assessment of the architecture of a lesion compared with light microscopy. A recent non inferiority study compared reads of 299 breast cases by 4 pathologists, and found

no significant difference in the incidence of major discordances using digital microscopy versus light microscopy.[81]

Leeds Teaching Hospitals NHS Trust made the decision to pilot digital pathology for the primary diagnosis of breast histopathology specimens, utilising the novel validation protocol outlined in chapter 4. This protocol offered participant histopathologists digital microscopy training, exposure to challenging cases, and a risk mitigated early conversion to a full digital slide workload.

5.1.2 Methods

3 consultant breast histopathologists with 35 years of combined practice were recruited to participate in the validation study. Scanning of all breast histopathology glass slides prior to laboratory send out was initiated prior to the study period, as part of the departmental digital pathology deployment roadmap. Scanning was performed using a single Aperio AT2 scanner for standard dimension slides (Leica Aperio, Vista, US), and a single CS2 scanner (Leica Aperio, Vista, US) for large slides. Standard slides were scanned at 40x equivalent magnification, and large slides at 20x equivalent magnification, all with JPEG2000 compression. Automated scanning processes (selection of scanning area, placement of focus points) were quality checked and repeated manually by a laboratory technician where necessary.

Digital images were stored in a remote digital archive, along with relevant clinical information, including a scanned copy of the original request form, and retrieved using e-Slide Manager software (Leica Aperio, Vista, US). Images were viewed by

consultant pathologists using Leeds Virtual Microscope viewing software (University of Leeds, Leeds TH NHS Trust) on medical grade Coronis Fusion 6 MP, 30.40 inch screens (Barco, Kortrijk, Belgium). (See figure 12 for an image of a digital pathology workstation using during the validation)

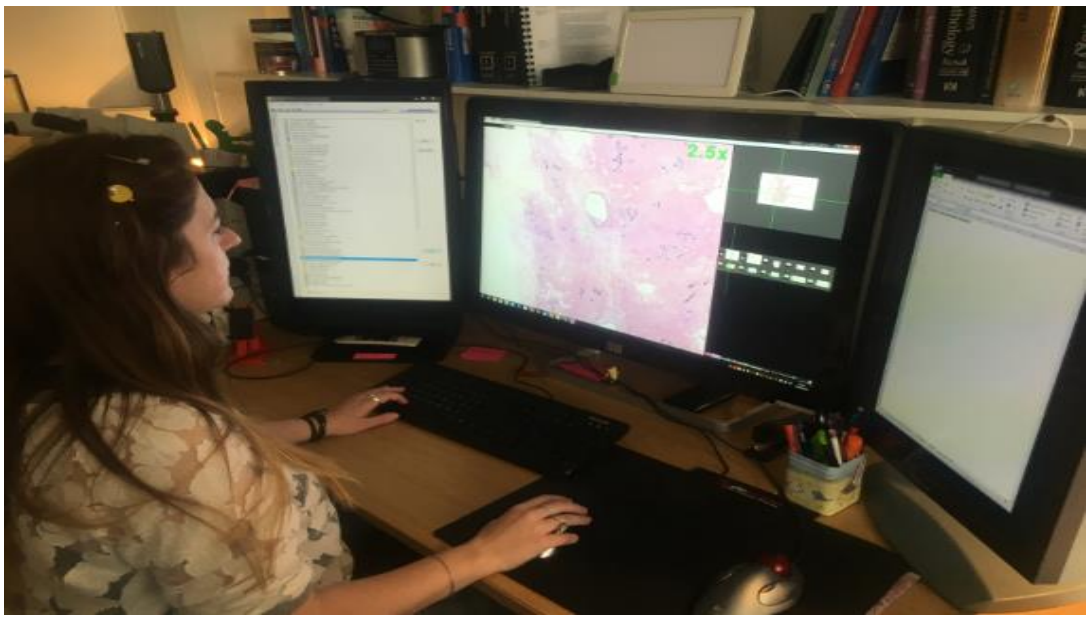

Figure 12. A digital pathology workstation in use during the breast histopathology validation. The central screen is medical grade, and used for slide viewing. The screens to either side are used to display patient information in the LIMS, and the reporting software.

The validation structure consisted of 3 phases, a training phase (T), a validation training set phase (V1), a live reporting validation phase (V2) and a summary phase (S). (See table 13 in chapter 4 for an overview of the validation procedure).

Prior to the initiation of training, each participant completed a questionnaire detailing their prior experience of, and attitude towards digital pathology. The pathologists expressed a range of views, with one expressing strong enthusiasm for digital pathology, one admitting they were sceptical, and one uncertain about their attitude to digital reporting.

5.1.2.1. Training Phase (T1)

In T1, each participant received a one hour individual session in basic use of the digital pathology slide viewer (LVM)[10], and the image management software (e-Slide Manager, Leica Aperio), and was issued a user manual. Participants were observed opening and evaluating cases, and given feedback regarding effective use of input modalities (mouse and keyboard shortcuts). Participants could request additional training as required, but none elected for this.

5.1.2.2 Validation 1 – Training set (V1)

In V1, each participant received a training set of 20 breast histopathology cases, in glass slide and digital slide formats. The training set was designed to encompass the breadth of breast diagnosis, and confront the participant with cases which might be challenging to diagnose digitally. The cases were chosen based on clinical relevance to our department, and the challenging digital cases were selected based on my systematic analysis of digital discordance (chapter 3). The cases are detailed in table 14. Participants viewed the training set in their own time. For each case, the digital slides were viewed first, then the pathologist recorded their diagnosis, and their level

of confidence in their diagnosis, on a Likert scale from 1-7, where 1 corresponded to no not at all confident, and 7 to very confident.

The pathologist then viewed the glass slides for the same case, immediately after the digital read, and recorded any alteration in their diagnosis, and their confidence in their glass slide diagnosis. When all participants had completed the training set, the results were discussed in a group with the researcher, and all participants reviewed discordant cases on glass and digital slides. Pathologists identified the types of case they found problematic on digital, so that they could ensure they were vigilant for these type of error in the next phase, V2.

Case	Diagnosis	Domains explored
1	Benign phyllodes tumour	Diagnosis (benign fibroepithelial)
2	Fibrocystic change, weddelite calcification	Diagnosis (benign tissue), identification of weddelite calcification
3	Fat necrosis	Diagnosis (benign/inflammatory condition)
4	Sparse residual ductal carcinoma, post chemotherapy	Diagnosis (malignant epithelial), grading, immunohistochemistry interpretation (sparse tumour cells)
5	Invasive ductal carcinoma, grade 2, neuroendocrine features	Diagnosis (malignant, epithelial), grading, immunohistochemistry interpretation, identification of neuroendocrine features
6	High grade ductal carcinoma in situ with small, grade 1 invasive component	Diagnosis (malignant epithelial)grading, identification of small invasive component
7	Atypical ductal hyperplasia, flat epithelial atypia, microcalcification, sclerosed papilloma	Diagnosis (benign and atypical epithelium, papillary lesion), identification of microcalcification
8	Invasive ductal carcinoma, grade 3	Diagnosis (malignant epithelial) grading, immunohistochemistry interpretation

9	Paget's disease of nipple	Diagnosis (malignant epithelium), immunohistochemistry, special stain interpretation
10	Fibroadenoma with ductal carcinoma in situ	Dual diagnosis (malignant epithelium and fibroepithelial lesion)
11	High grade ductal carcinoma in situ, no calcification	Diagnosis (malignant epithelial), grading, identification that no calcification is present
12	Benign sclerotic lesion	Diagnosis (benign lesion), immunohistochemistry interpretation
13	5mm lymph node metastasis	Diagnosis (locate metastasis)
14	Organising haematoma	Diagnosis (benign/inflammatory)
15	Apocrine metaplasia with atypia	Diagnosis (borderline lesion)
16	Lymph node with micrometastasis	Diagnosis (locate micrometastasis)
17	Nipple dermatitis	Diagnosis (benign dermatosis)
18	Mucinous carcinoma, grade 1	Diagnosis (malignant epithelial), grading, identification of mucin
19	Pleomorphic lobular carcinoma, grade 2	Diagnosis (malignant epithelial), grading, identification of pleomorphic lobular content
20	Invasive lobular carcinoma, grade 2	Diagnosis (malignant epithelial), grading, identification of classic lobular features

Table 14. Training cases for breast histopathology primary digital diagnosis

5.1.2.3 Validation 2 – Live cases (V2)

In V2, the totality of each participants breast pathology workload was scanned prospectively. The pathologists made their primary diagnoses on digital slides, recording them in a spreadsheet, along with their confidence in their diagnosis, expressed on a 7 point Likert scale. All cases were then checked on glass before final reporting, and any modification to the diagnosis was recorded, along with the glass slide confidence in diagnosis, and the preferred diagnostic medium for each case. Pathologists were also asked to record any technical failures – i.e. out of focus digital

slides, or those with any digital artefact which might preclude confident or safe diagnosis.

All discordances were discussed at weekly to fortnightly validation meetings, were digital and glass slides were reviewed by all available participants and the researcher. When each participant had viewed 2 months whole time equivalent workload (estimated at approximately 200 cases based on departmental data), their diagnostic spreadsheets were analysed by the researcher, and concordance and discordance data was summarised. This data was discussed between each participant and the researcher, and the scope of that pathologist's future digital pathology practice was agreed upon, with specific criteria documented for cases which require a check on glass before final sign out.

5.1.3 Results

5.1.3.1 Validation 1 – Training set (V1)

Each participant viewed the same 20 training cases on digital slides and glass, consisting of 60 slides in total. Mean diagnostic concordance for all participants was 92% (range 80% - 100%). Discordant cases concerned the following areas of diagnosis: mitotic count component of invasive tumour grading, failure to detect weddelite calcification, micrometastasis detection, and the recognition of ductal atypia. (see figure 13 for examples of discordant cases from the training phase of the validation.)

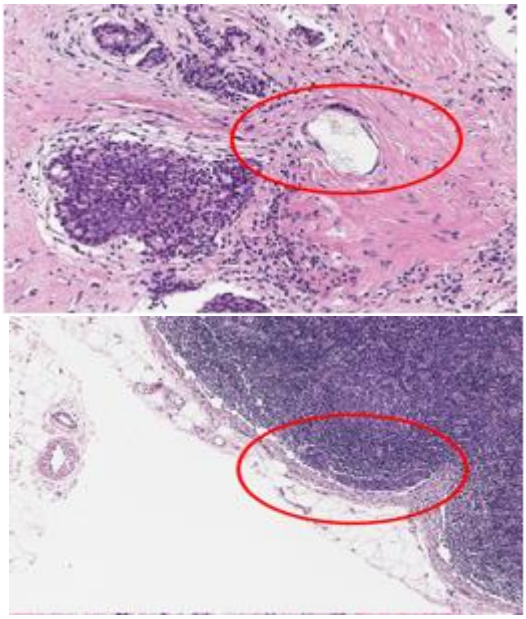

Figure 13. Missed diagnostic objects. Top image shows weddelite calcification, and bottom image a micrometastasis, both missed by multiple participants in the V1 stage of validation.

5.1.3.2 Validation 2 – Live cases (V2)

The three participants viewed a total of 694 complete breast histopathology cases, consisting of 15,000 slides. The cases were representative of the specimen type and diagnostic category mix found in the departmental breast workload. (See tables 15 and 16).

Specimen type	Number of cases
Vacuum assisted biopsy	159
Core biopsy	397
Wide local excision	28
Mastectomy	27
Other excision	55
Immunostains/special stains only	28
Total	**694**

Table 15. Specimen types included in the V2 caseload.

Diagnostic category	Number of cases
Normal tissue	85
Benign lesion	308
Lesion of uncertain malignant potential	51
Suspicious	5
Malignant – in-situ	43
Malignant – invasive	145
Lymph node specimen – no lymphoid tissue	1
Lymph node specimen – benign lymphoid tissue	22
Lymph node specimen – malignant, metastatic carcinoma or other	5
Other	29
Total	**694**

Table 16. Types of diagnosis included in the V2 caseload.

In the course of the validation, a technical failure rate of 1.0% was observed - these were cases where scanning artefact or focus issues with digital slides resulted in the pathologist rejecting the digital slides and making a diagnosis on glass. There was complete clinical concordance between the glass and digital impression of the case in 98.8% of cases. Only 1.2% of cases had a clinically significant difference in diagnosis/prognosis on glass and digital slides. (See table 17)

	Pathologist 1	Pathologist 2	Pathologist 3	All pathologists
Technical failure rate (%)	0.7	1.4	1.0	**1.0**
Complete concordance (%)	95.0	96.2	97.4	**96.2**
Any observable difference (%)	5.0	3.8	2.6	**3.8**
Complete clinical concordance (%)	99.3	99.1	98.5	**98.8**
Clinically significant observable difference (%)	0.7	0.9	1.5	**1.2**

Table 17. Pathologist concordance and discordance percentages in V2.

All discordances were reviewed on glass and digital by the validation group and trainer. Clinically significant discordances concerned the mitotic count component of invasive tumour grading, identification of weddelite calcification, identification of isolated tumour cells, assessment of a fibroepithelial lesion for cellularity, and identification of focal epithelial atypia. (See figure 14 for example images).

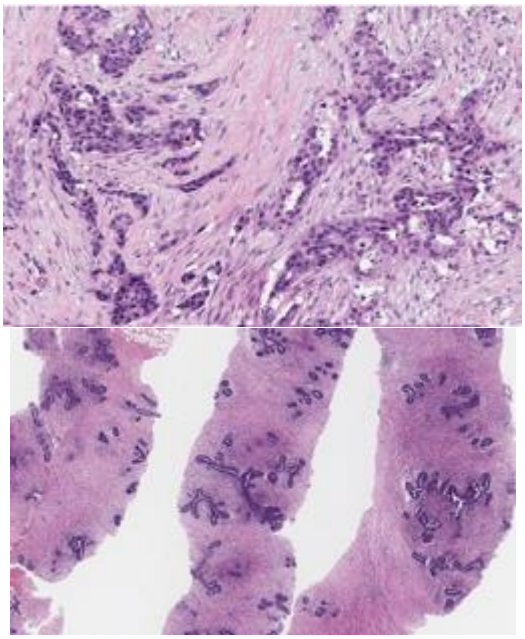

Figure 14. Slides that were difficult to interpret on the digital microscope. Top – a tumour in which a participant had difficulty identifying mitotic figures and bottom – a fibroepithelial lesion, both of which were difficult to assess on digital slides.

The 2 most significant discordances both concerned the diagnosis of DCIS. In one case, a small focus of DCIS was missed on the digital read of an otherwise B3 screening case, whilst in another case, a small focus of DCIS was correctly diagnosed on the digital slide in a large, multi-slide case, but missed on the initial glass review of the case. The pathologist had to revert to the digital case to locate the corresponding glass slide, and was then able to identify the DCIS on the glass, which had been overlooked. Use of glass slides only for this case could have resulted in misclassification of a B5a case as B2. (See table 18).

Specimen	Digital diagnosis	Glass slide diagnosis	Preferred diagnosis (gold standard)
Core biopsy	Grade 2 invasive ductal carcinoma	Grade 3 invasive ductal carcinoma	Glass
Vacuum biopsy	Benign phyllodes tumour	Fibroadenoma with inflammation	Glass
Vacuum biopsy	Columnar cell change	Columnar cell change plus atypical intraductal proliferation	Glass
Vacuum biopsy	Sclerosing adenosis	Sclerosing adenosis, small focus of ductal carcinoma in situ	Glass
Vacuum biopsy	Microcysts	Microcysts and weddelite calcification	Glass
Vacuum biopsy	Benign	Isolated tumour cells	Glass
Vacuum biopsy	Columnar cell change	Columnar cell change, single focus of atypical cells	Glass
Vacuum biopsy	Small focus of ductal carcinoma in situ	Benign	Digital

Table 18. Clinically significant discordances documented during V2.

5.1.3.3 Diagnostic confidence and diagnostic modality preference

Mean diagnostic confidence (on a Likert scale from 0-7) was similar for each pathologist for digital slides and for glass slides. (See table 19), although the range of diagnostic confidence scores was dramatically different for one pathologist (0-7 on digital, versus 6-7 on glass).

	Digital Slides		Glass slides	
	Mean confidence (0-7)	Range	Mean confidence (0-7)	Range
Pathologist 1	6.70	4-7	6.80	4-7
Pathologist 2	6.90	4-7	6.90	4-7
Pathologist 3	6.79	0-7	6.99	6-7

Table 19. Pathologist confidence in digital and glass slide diagnosis in V2

All of the participant pathologists identified a proportion of cases for which they preferred to use glass slides over digital slides, although digital slides were judged to be superior or equivalent to glass slides in the vast majority of cases. (See figure 15) Cases where glass slides were preferred all involved mitotic counting, weddelite detection and lymph node searches.

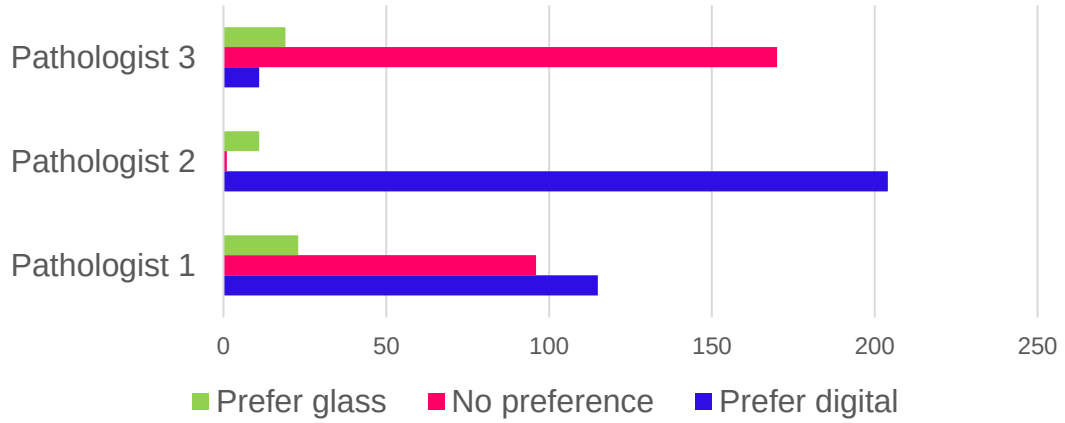

Figure 15. Pathologist reporting modality preferences in V2. For each case in the validation, pathologists recorded if they preferred the glass or digital to make their diagnosis, or had no preference.

5.1.3.4 Beliefs about digital pathology efficiency

Prior to their validation procedure, the pathologist group predicted that viewing digital slides would be slightly slower than viewing glass slides, and that breast

resections would be much slower to report on digital. After the validation procedure, the pathologists reported that they perceived their digital reads of resection cases and large/multi-level biopsies to be much faster using digital slides rather than glass slides, and resections to be either slightly faster or much faster on the digital microscope.

Prior to the validation procedure, pathologists believed the most relevant barriers to digital pathology adoption were increased time to view digital slides compared with glass slides, pathologists' lack of exposure to digital pathology and pathologists' resistance to change. Following the validation procedure they identified the chief barriers to digital pathology adoption were financial cost to the department and the time taken to scan slides in the laboratory.

When asked to list the principal benefits of digital slides over glass slides, pathologists listed ease of access to previous biopsies/linked specimens, more efficient diagnosis of large cases/multi slide biopsies, diagnostic utility of the low power overview of the slide, more efficient delivery of digital slides to the pathologists desktop, enhanced opportunities to teach trainees and ergonomic benefits.

5.1.4 Discussion

Digital pathology has the potential to transform the way in which breast pathology services are delivered. Rapid transfer of images across geographical boundaries can allow for more efficient dispersal of pathology workload between linked hospitals, and make best use of pathologist manpower. Rapid access to second opinion on challenging cases, and increased collaboration between pathologists on cases could lead to significant improvements in the quality of pathology diagnosis.

Successful adoption of digital pathology for primary diagnosis in a department is dependent on individual pathologists, many with decades of experience reporting on a light microscope, engaging with a new technology, educating themselves on its limitations, and actively learning how to use software and hardware efficiently. As with the adoption of any new diagnostic procedure, patient safety should be paramount. The US Food and Drugs Administration guidance to manufacturers recommends that medical devices (including whole slide imaging systems) should be able to demonstrate established safety and effectiveness.[82] The digital pathology guidelines published by the Royal College of Pathologists also describe the need for individual pathologists to be validated with sufficient rigour to satisfy an internal or external observer that safety and clinical effectiveness are maintained. The document also emphasises that validation should occur in a real world context. This study documents the first instance of use of the novel validation and training protocol for digital primary diagnosis of histological specimens, which has since been recommended as an example of best practice in the Royal College of Pathologist's Guidelines for Digital Pathology [1].

The philosophy of this validation protocol is slightly different from the approach of the College of American Pathologists (CAP) Guideline[74] and of other non-inferiority studies, largely because of the intended purpose of the validation procedure. The CAP validation intends to validate that a WSI system produces images of sufficient quality for correct diagnoses to be made. The aim of the Leeds validation protocol is to allow individual pathologists to validate their own digital slide practice against their conventional light microscopy practice. The protocol is centred on the individual pathologist rather than a department as a whole, and it is competence driven rather

target driven. This approach takes into account the variability in IT competencies, diagnostic experience and enthusiasm for technology between pathologists, and allows all members of a department, whether enthusiasts or sceptics to develop digital pathology skills and gain confidence in their abilities. Three specialist breast pathologists viewed 694 complete “live” breast cases, including large format slides, stained with haematoxylin and eosin, immunohistochemistry and special stains. Complete clinically significant concordance was observed in 98.8% of cases, indicating excellent agreement between digital primary diagnosis and glass slide review. Our findings suggest that pathologists, given access to digital pathology training, and a risk mitigated diagnostic environment to gain real world digital reporting experience, can competently and confidently use digital pathology for primary diagnosis as standard practice.

The training and validation process allowed the participant pathologists to identify and discuss areas of digital diagnosis they found more challenging, and identify subtypes of breast case which warrant glass review of digital slides, in order to maintain patient safety and allow for further education of the pathologist and navigation of specific learning curves (eg. for confident identification of mitotic figures or navigation of lymph nodes). Identification and counting of mitotic figures was consistently highlighted as an area of difficulty for pathologists. Our pathologists perceived two causes of this difficulty in digital reporting: firstly they suggested that less contrast between chromatin and the background on digital slides made mitoses harder to identify, and secondly, they were unable to fine focus on suspected mitotic figures on digital slides, a function they often perform on glass slides to confirm the identity of mitoses. A number of workarounds and strategies to mitigate this

difficulty could be considered, including use of immunohistochemistry to highlight mitoses, the use of image analysis software to automate mitotic counts, or mandatory checks of mitotic count on glass slides prior to specimen sign out, in cases where mitotic score would affect overall grading of an invasive tumour.

Our pathologists reported perceived greater efficiency in reporting multi-slide biopsies and large resections on digital slides, which they attributed to a number of factors. This was partly because they no longer had to load and reload glass slides on the microscope stage, and could move swiftly between slides. In addition, they found the full screen low power view of individual slides enabled them to assess lesional architecture with greater ease, and they were able to make measurements using digital tools efficiently and accurately. The relative diagnostic efficiency of pathologists using digital versus glass slides deserves further attention, especially now that there is a growing cohort of pathologists with significant digital microscopy experience to compare fairly with conventional light microscopy . Others benefits of digital reporting noted by our pathologists included rapid access to previous biopsy specimens when reviewing resections, more engaging education and training of junior colleagues, and ergonomic benefits.

As a consequence of this validation study, our validated breast pathologists now report all cases on digital slides as standard, reverting to glass following digital examination only for cases fulfilling set criteria (invasive cancers where differences in mitotic score could affect overall grade, cellular fibroepithelial lesions, cases with radiological confirmation of calcification but no calcium identified on digital, and any challenging case not encountered in the validation phase.) On the basis of the validation pilot in breast pathology, it was decided that the laboratory at Leeds

Teaching Hospitals NHS Trust would commence scanning all histopathology slides for all specialties, and that all consultants would complete a validation procedure for the relevant diagnostic subspecialty. As the validation process is completed for each specialty, more data can be gathered on challenging areas of digital diagnosis. It is important that individual departments share their experiences with digital pathology, and highlight areas of potential difficulty which can be prioritised in the digital training of their colleagues to ensure a safe transition from glass slide to digital slide reporting.

5.2 Validation of neuropathology for primary diagnosis

Following a successful pilot in primary digital diagnosis of breast histopathology, Leeds Teaching Hospitals NHS Trust decided to initiate training and validation in primary neuropathological diagnosis and frozen section evaluation.

5.2.1 Background

As arguably one of the most specialised diagnostic topographies, and with only 70 practitioners in the UK[83], neuropathology stands to benefit a great deal from digitisation. Networked digital pathology systems allow more flexibility in who reports what and where, and can help ensure that complex histology slides are transferred to a suitably experienced neuropathologist for frozen section analysis, primary diagnosis or secondary opinion instantaneously, regardless of the geographical location of the specimen.

There is little data regarding diagnostic safety in digital neuropathology, as the majority of published validation studies have excluded neuropathology specimens,

or only included them in small numbers.[38] One multi-specialty study identified a single major discrepancy between glass and digital diagnoses, which related to a neuropathology case.[57] A pilot digital neuropathology study [84] found individual digital:glass concordance rates for two neuropathologists of 94.9% and 88%, and identified two common causes of glass:digital discrepancy: identification of mitoses and assessment of nuclear detail.

5.2.2. Methods

The study was performed in the histopathology department of St James University Hospital, Leeds, UK, a major NHS cancer centre. Leeds provides neuropathology and ophthalmic pathology services to the West Yorkshire region, encompassing a population of approximately 3 million, and includes multidisciplinary team meetings for adult, young adult and paediatric central nervous system tumours, and adult and paediatric neurology. The department receives approximately 2750 brain, ophthalmic, nerve and muscle specimens per annum, and an additional 300 frozen sections. The department's two specialist neuropathologists, with combined consultant experience of 34 years (20 years and 14 years) were recruited to train in digital diagnosis, and validate their primary diagnostic practice using a digital pathology system.

5.2.2.1 Primary diagnostic validation

All neuropathology histopathology glass slides, including H and E, immunohistochemistry and special stains were scanned prior to laboratory sign-out, before distribution to participating pathologists. All slides were scanned on one of six Aperio AT2 scanners. (Leica, Vista, CA, US). Standard H and E and special stains were

scanned at x40 equivalent magnification, whilst immunohistochemistry was captured at x20 equivalent magnification.

Automated tissue detection and scanning point placement provided by the scanner were utilised, and quality checked by the scanner operator (a trained biomedical scientist) as per departmental protocol. The diagnostic images were stored in a remote digital archive, and retrieved with e-Slide Manager software (Leica, Vista, CA, US). The scanner operator performed a final quality control check on the captured images to detect scanning artefact and major focusing issues. Images were viewed by consultant neuropathologists using Leeds Virtual Microscope slide viewing software (University of Leeds, Leeds TH NHS Trust, UK) on medical grade 8 MP screens (Eizo, Hakusan, Japan). Figure 16 depicts one of our neuropathologists at work on their digital workstation during their validation.

Figure 16. A neuropathologist at work during their validation. The slide is viewed on an 8 Megapixel medical grade screen.

The validation protocol described in chapter 3 was utilised, consisting of a training phase (T), Validation – Training Cases (V1), Validation – Live reporting (V2) and summary phase (S).

5.2.2.3 Training Phase

The training phase, (T), consisted of an hour-long individual session covering basic digital pathology skills including use of the image management software (e-slide manager) and the viewing software (Leeds Virtual Microscope). Participants were observed opening and navigating cases, and were given feedback regarding their use of input modalities (gaming mouse ergonomics and use of keyboard shortcuts). Participants were able to request additional training as required, and provided with user manuals for the software, and standard operating procedures for the validation protocol and for departmental digital reporting.

5.2.2.4 Validation 1 - Training Set (V1)

In V1, each pathologist received a training pack consisting of a set of 20 challenging and educational neuropathology cases, all presented in both digital slide and glass slide formats. The training set was designed to encompass a broad range of diagnoses and tissue types, and to expose the pathologist to types of case that might be problematic to a novice digital diagnostician. The cases selected are documented in table 20. All cases/ specimen types selected which were relevant to departmental practice, and the challenging cases were selected based on my review of the relevant discordance literature for neuropathology (chapter 3).[4]

Participants were allowed to take as long as they needed to complete the training set comfortably. Pathologists were asked to view the digital slides first for each case,

recording both their diagnosis, and their confidence in that diagnosis (on a Likert scale from 1-7, where 1 corresponded to not at all confident, and 7 to very confident) in a workbook, which also contained the relevant clinical details for the case. Pathologists then viewed the glass slides for the case immediately after the digital read, and recorded any alteration in their assessment of the case, as well as their confidence in their glass slide diagnosis.

Following completion of the training set by both participants, the results were discussed in a group with the trainer, and all participants reviewed cases that had caused difficulty. Pathologists identified the types of case they found problematic on digital slides, and progressed to the next phase, V2, armed with this information.

Case	Diagnosis	Domains explored
1	Oligodendroglioma	Diagnosis, grading
2	Metastatic carcinoma - breast primary	Diagnosis, immunohistochemistry interpretation
3	Schwannoma	Diagnosis
4	Pilocytic astrocytoma	Diagnosis
5	Giant cell glioblastoma multiforme	Diagnosis, grading
6	Diffuse astrocytoma	Diagnosis, grading
7	Pituitary adenoma	Diagnosis, immunohistochemistry interpretation
8	Epithelioid GBM	Diagnosis, grading
9	Metastatic carcinoma - lung primary	Diagnosis, immunohistochemistry interpretation
10	Pituitary adenoma	Diagnosis, immunohistochemistry interpretation
11	Rhabdoid meningioma	Diagnosis, subtype recognition, grading
12	Anaplastic glioma WHO Grade 2	Diagnosis, grading
13	Lymphoma	Diagnosis, atypical lymphocytic proliferation identification
14	Myositis	Diagnosis, special stain interpretation
15	Temporal arteritis	Diagnosis, granuloma detection
16	Giant cell glioblastoma multiforme	Diagnosis, subtype recognition
17	Acute and chronic inflammation. No evidence of malignancy.	Diagnosis, confident exclusion of malignancy

18	Microcystic meningioma	Diagnosis, subtype recognition
19	Mature teratoma	Diagnosis, tissue type recognition
20	Benign melanosis - conjunctival specimen.	Diagnosis, benign melanocytic lesion

Table 20. Validation training cases for neuropathology primary diagnosis

5.2.2.5 Validation 2 - Live Cases (V2)

In V2, all departmental neuropathology cases were scanned prospectively. The pathologists made their live primary diagnosis on the digital slides, and recorded the diagnoses, and their diagnostic confidence on an Excel spreadsheet. All cases were then reviewed on glass prior to final sign out, and any modification to the digital diagnosis was recorded, in addition to the pathologist's confidence in the glass slide diagnosis. A record was also kept of any technical failures – e.g. out of focus regions on slides or the presence of digital striping artefact.

When each pathologist had viewed approximately 2 months whole time equivalent workload (estimated at 150 histology cases on the basis of departmental data), their diagnostic spreadsheet was analysed, and concordance and discordance data were summarised (Summary phase - S). These data were discussed with the participant, and the scope of that pathologist's future digital pathology practice was agreed upon.

5.2.3 Results

5.2.3.1. Validation 1 – Primary diagnostic training set (V1)

Each participant viewed the same training set of 20 neuropathology cases on digital slides and glass slides. The diagnostic concordance between digital and glass slide reads was 85% (17/20) for both participants. The discordances encountered are described in table 21, and frequently concerned mitotic figure detection and grading.

In all cases of discordance, group review of the glass slides confirmed that these held the ground truth diagnosis.

Participant	Case number	Digital slide diagnosis	Glass slide diagnosis	Comment
1	8	Likely reactive, differential diagnosis to include GBM	Definite GBM	Mitoses hard to see on digital. GFAP difficult to interpret, very dark on digital.
1	11	Meningioma (WHO 1)	Atypical Meningioma (WHO 2)	On digital read, missed focal pleomorphic cells and mitoses.
1	12	Diffuse glioma, unable to grade	High grade glioma	On digital read, mitoses difficult to assess, nuclei very dark.
2	6	Diffuse glioma/astrocytoma WHOII	Anaplastic glioma/astrocytoma WHO III	Mitotic figures difficult to discern on digital – nuclei very dark.
2	8	Glioblastoma multiforme WHO IV, epithelioid component	Glioblastoma multiforme, WHO IV	Vascular proliferation mistaken for epithelioid component on digital
2	12	Anaplastic glioma (WHO II)	Anaplastic glioma (WHO III)	Mitotic figures difficult to discern on digital

Table 21 . Discordant cases from the training phase of validation.

5.2.3.2 Primary Diagnosis Validation 2 – Live cases (V2)

The participants viewed 340 complete neuropathology cases between them. The cases were representative of the specimen type and diagnostic category mix found in the departmental neuropathology workload, and included diagnostic biopsies and excisions, and included brain, muscle, nerve and ophthalmic specimens.

The pathologists had to defer full digital assessment in 16 cases due to quality issues. These instances all related to muscle biopsies, and in all cases the haemotoxylin and eosin slides were assessable on digital, but the crucial Gomori and ATPase stains were unreadable. (See figure 17 for an example.)

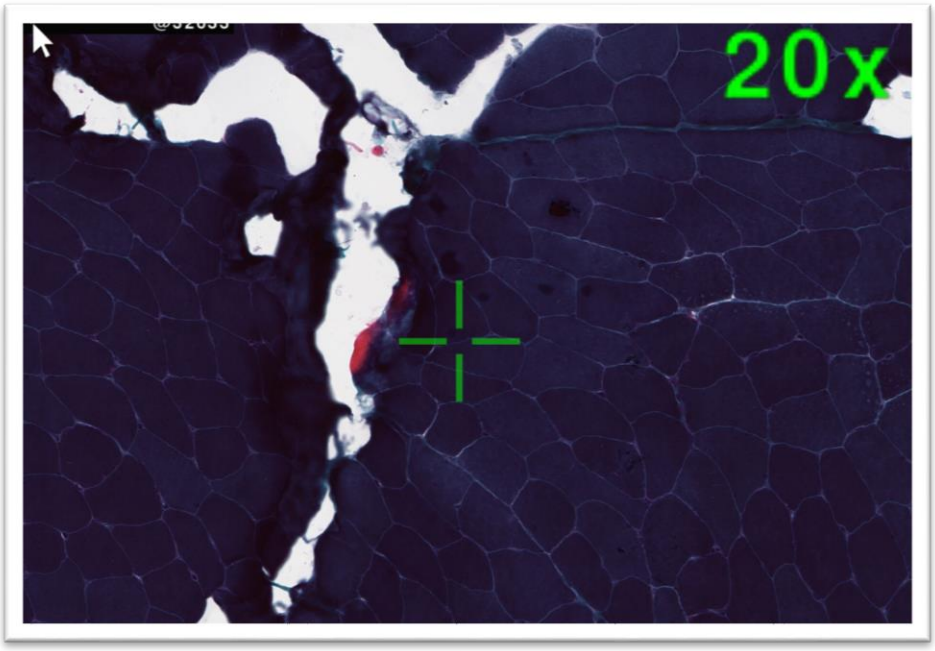

Figure 17. Example of a digital slide of Gomori stained muscle which could not be interpreted. The slide was too dark for the contrasting stain to be seen.

When these cases are excluded from the total, there was complete clinical concordance between the glass slide and digital slide reads in 98.1% of cases (318/324). Only 1.8% of cases had a clinically significant difference with the potential

to affect diagnosis/prognosis between digital and glass slide reads. See table 22 for a breakdown of concordance statistics for the 2 pathologists.

	Pathologist 1	Pathologist 2	Combined
Total number of cases	125	215	340
Technical deferral to glass	9	7	16
Clinically significant observable difference	2	4	6
Complete diagnostic concordance	98.3% (114/116)	98.1% (204/208)	98.1% (318/324)

Table 22. Live reporting validation statistics

All discordant cases were reviewed on glass and digital by the participant and the trainer. In all cases, the glass slides were judged to hold the ground truth. Clinically significant discordances concerned identification of mitotic figures, and confident identification of malignant lymphoid proliferations. (See table 23 for a summary of all discordances.) (See figure 18 for an example).

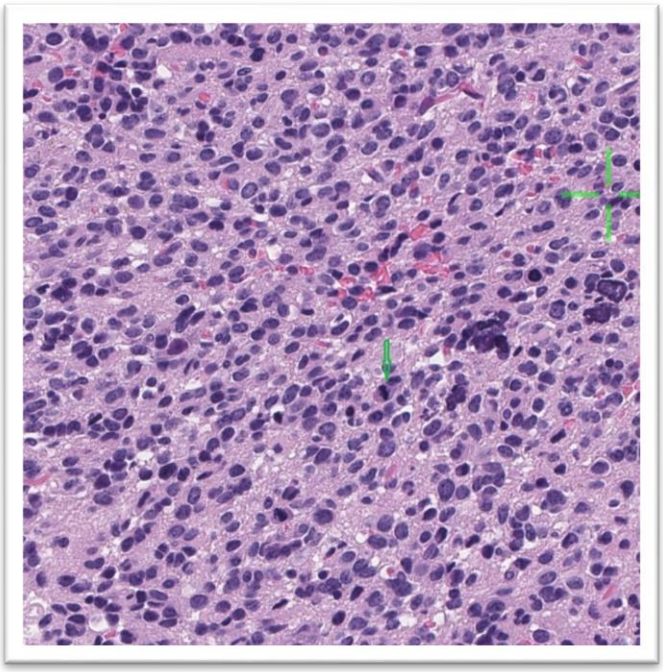

Figure 18. Example of a digital slide of a brain tumour where identification of mitotic figures was challenging. The green arrow indicates a mitotic figure which was not identified on the initial digital assessment of the case.

Digital diagnosis	Glass diagnosis	Comment
Low grade glioma	High grade glioma	Mitotic figures difficult to discern on digital
Small round blue cell tumour	Lymphoma	Malignant lymphoid cells clearer on glass slides
Astrocytoma WHO 3	Glioblastoma multiforme WHO 4	Mitotic figures difficult to discern on digital
Meningioma	Atypical meningioma	Mitotic figures difficult to discern on digital
Glioma WHO 2	Glioma WHO 3	Mitotic figures clearer on glass
Lymphoid tissue - ??malignant/?? reactive	Malignant lymphoid proliferation consistent with lymphoma	Nuclear features/fine detail clearer on glass slides

Table 23. Discordant cases from the live reporting phase of validation (V2)

5.2.3.3 Diagnostic confidence and diagnostic modality preference

The mean diagnostic confidence, on a Likert scale from 1-7 was similar for each pathologist for digital slides and for glass slides (see table 24), although the range of diagnostic confidence varied between digital and glass. Both pathologists detected a proportion of cases (4% for pathologist 1, 3% for pathologist 2) where they clearly preferred the glass slide presentation of the case. These cases all involved borderline mitotic counts.

Pathologist	Mean diagnostic confidence on digital	Mean diagnostic confidence on glass
1	6.7 (Range 3-7)	7.0 (Range 7-7)
2	6.9 (Range 5-7)	7.0 (Range 6-7)

Table 24. Pathologist diagnostic preferences

5.2.4. Discussion

Digital pathology is a transformative technology, with the potential to revolutionise the way in which neuropathology services are delivered. Digitisation of slides allows for rapid transferability, enabling the establishment of robust, efficient diagnostic networks for intra-operative diagnosis and consultations. In addition to streamlining diagnosis and referral, remote reporting of scanned slides could allow more equitable access to specialised neuropathological opinion. It is also likely that digitisation of the specialty could aid recruitment and retention of neuropathologists, by supporting flexible and remote working.

This study documents the first use of the Royal College of Pathologists' approved validation and training protocol[1] for the diagnosis of neuropathological specimens. This approach is focussed on the training needs of the individual pathologist, and is competence driven rather than target driven. Two specialist neuropathologists viewed 340 complete neuropathological cases, including H and E,

immunohistochemistry and special stains. Complete clinical concordance was observed in 98.1% of cases, indicating excellent agreement between digital primary diagnosis and glass slide assessment. This statistic is similar to the published validation findings using the same protocol for breast histopathology (see above).[85] Our findings suggest that suitably trained and validated pathologists can competently and confidently use digital pathology for standard primary neuropathology reporting practice.

Our pathologists reported a number of key benefits to digital reporting, including:

- Instantaneous access to previous biopsies in the digital archive for comparison with new metastases, and ability to compare these directly on screen.
- Greater efficiency assessing multi-slide cases, especially cases with large immunohistochemistry panels.
- Easier navigation between small pieces of tissue on a slide for fragmented specimens.
- More efficient preparation and selection of cases for multidisciplinary team meetings (MDTM) and tumour boards.
- More secure, convenient MDTM and tumour boards. (Negating the need to physically transport glass slides from the histopathology department to the MDT suite in a separate institution.)
- Enhanced training experience for junior pathologists and trainees. Pathology trainees can be directed towards neuropathology cases with optimum educational value in the digital slide archive, facilitating more equitable distribution of training cases between a training group, and allowing the

trainer to personalise cases to the needs of the trainee. Use of digital slides by the consultant histopathologist frees the glass for the student, who can study them, or the digital slides at leisure, without compromising turn-around times for the patient by delaying definitive diagnosis.

- Review of digital slides allows for a more engaging teaching experience, and allows a single pathologist to interact with a group of trainees, gathered around a screen, without the need for a multi-headed microscope.

In the course of their validation procedure, our pathologists identified key areas of digital reporting they found more difficult on digital slides, particularly in the early stages of the validation, and both appreciated a “learning curve” for mitotic figure detection in particular. Two causes for this can be proposed: firstly an observation that there was less contrast between chromatin and the nuclear background on digital slides, rendering the nuclei dark and difficult to interpret, and secondly the inability to adjust the fine focus of potential mitotic figures. In our experience, our validation procedure of direct comparison of digital and glass slide images allowed our pathologists to reconcile the appearance scanned mitoses with the glass slide image, and they soon gained confidence in digital mitotic scoring. Given the initial difficulty, and the importance of mitotic scoring in accurate tumour grading, the group decided that post-validation, any cases with “borderline” mitotic counts should be reviewed on glass before sign out, to ensure maintenance of diagnostic quality. In the future, the use of image analysis software could support the work of the pathologist by providing rapid, reproducible mitotic scoring for scanned digital pathology slides.

Since completion of the validation period in 2018, our neuropathologists now report all cases on digital slides as standard, deferring to glass slides only when they wish to confirm mitotic count in borderline lesions, or where special stains are too dark for easy digital assessment.

5.3 Conclusion

In this chapter, the results of two digital pathology validation pilots are presented – for breast and neuropathological primary diagnosis. Specialist pathologists working in both topographies were able to achieve high levels of diagnostic concordance between their glass slide and digital slide histology interpretations, and both cohorts of pathologists now practice digital pathology as standard at Leeds Teaching Hospitals NHS Trust. Interestingly, both groups of pathologists could identify areas of digital practice in which they still lacked confidence following their validation period, and elected to mandate glass slide checks of particular cases. Following completion of the two pilots, it was decided that Leeds Teaching Hospitals would roll the protocol out to all remaining histopathology subspecialty reporting groups (Gastrointestinal, hepatobiliary, skin and soft tissue, cardiothoracic, gynaecological, urological and head and neck), who are currently in the process of V1 and V2 phases of validation. Pathologists are progressing at different rates, reflecting differing levels of comfort with IT, and acceptance of digital pathology. One issue that has emerged is the extra time commitment that validation requires from the participant. Our pilot pathology groups estimated that the validation process required an additional 10% WTE for completion of the protocol. This time includes performing additional glass slide “safety checks” before signout of V2 cases and completing data collection

sheets documenting cases viewed and concordance/discordance rates. Some of the pathologists that started the protocol more recently are reporting an approximate doubling of time in their diagnostic sessions, attributable to “double reading” of cases on the digital and light microscope. This extra workload commitment would be unacceptable to the pathologist population, and result in major backlogs in a clinical department. Discussion with these pathologists revealed that they were completely re-reading every case in its entirety on glass slides following their initial digital slide read. Advice was re-issued to pathologists that after a few initial weeks of familiarisation, when they may want to check every slide, only the index slides pertinent to the diagnosis need to be reviewed on glass, or cases where the diagnosis is very uncertain on the digital read.

All the pathologists involved in the pilot were able to recognise key benefits of digital pathology in their clinical area, and were keen to expand their use of WSI to applications beyond the primary diagnosis of histology, including frozen section assessment and MDT presentation for the neuropathologists, and review of cytopathology specimens for the breast pathologists.

Chapter 6 Validation of digital diagnosis for non-primary diagnostic use cases

In the course of the Leeds Digital pathology deployment, it soon became apparent that there was a need to adapt the validation protocol for specific scenarios and use cases apart from primary diagnosis. Firstly, the author was approached by the neuropathologists who had taken part in the primary diagnostic validation pilot, who felt there was a clinical need for digital frozen section capability. Secondly, there was interest from both the laboratory and pathologists in streamlining access to immunohistochemistry slides, especially those requested as ancillary studies after assessment of the primary histology for the case. Re-uniting these slides with the relevant histology cases and sending them out to pathologists was viewed as cumbersome and time consuming, and the results of these tests were often needed in a short time frame for MDT presentation.

6.1 Frozen section assessment

Frozen section assessment is the process of providing an intra-operative pathological opinion on a biopsy. This could provide a differential diagnosis of an unexpected, incidental lesion, or provide the surgeon with feedback on completeness of lesional resection. In both scenarios a rapid assessment of a sub optimal histology slide is used to direct further surgical management of the patient rather than provide a definitive diagnosis. Preservation of nuclear and cytological detail is poor in a frozen section compared with conventional histology, and opinion is often based on grosser, architectural features.

6.1.1 A validation protocol for digital frozen sections

A simplified frozen section training programme was devised for the two neuropathologists who had already completed their primary diagnostic validation. Ten frozen section cases were selected from the glass slide archive, and scanned using an Aperio CS2 scanner (Leica, Vista, CA, US). This low throughput scanner was chosen for frozen sections because slides can be loaded and scanned without interrupting scanning programmes on the larger, high throughput scanners utilised for the primary diagnostic clinical deployment.

All slides were scanned at 40x equivalent magnification and subjected to JPEG2000 compression. Tissue detection software was not employed, so the entire scannable area of each glass slide was scanned, to ensure all tissue, however dispersed on the glass slide, was represented on the digital slide.

The ten cases were selected to represent commonly encountered frozen section scenarios in our department. Each pathologist was provided with the digital slides for each case, presented alongside all relevant clinical information available to the original reporting pathologist. The cases selected can be viewed in table 25. The pathologist was asked to make their frozen assessment on the digital slides, record this, and then immediately compare the digital slides with the glass slides for the same case, documenting any change in their assessment or their confidence in their report. Diagnostic confidence was measured using a 7-point Likert scale for both digital and glass slide reads.

Case	Archive frozen section report diagnosis	Ground truth following definitive evaluation
1	High grade astrocytoma	Gemistocytic astrocytoma
2	High grade glioma	Glioblastoma mulitforme
3	Suspicious for malignancy	Abscess/inflammatory lesion
4	Normal brain tissue	Normal brain tissue
5	Metastatic cancer	Metastatic squamous cell carcinoma
6	Meningioma	Meningioma
7	Malignant tumour	Glioblastoma multiforme
8	Inflammation	Benign inflammatory infiltrate
9	Low grade glioma	Pilocytic astrocytoma
10	Melanoma metastasis	Melanoma metastasis

Table 25. Frozen section training set. The neuropathology set consists of 10 cases covering a range of clinical scenarios.

6.1.2 Results

There was 100% clinical concordance between the digital slide and glass slide assessment of frozen section cases for each pathologist, and these assessments corresponded with the ground truth diagnoses obtained from examination of definitive histology. Pathologists demonstrated equal confidence in their digital and glass slide assessments of frozen sections.

As a result, both participant neuropathologists decided that digital slides could be used in place of glass slides for remote frozen section reporting in cases of clear clinical need, when no on-site neuropathologist is available. When a pathologist is on-site, it is more expedient to examine the freshly prepared glass slides, and this is the preferred option. To date, the neuropathologists have not needed to utilise digital slides for this purpose.

6.2 Immunohistochemistry assessment

The assessment and interpretation of IHC slides sometimes requires the pathologist to make a simple distinction between a positive and a negative result, but can be complex, requiring detailed localisation of the staining and correlation with the H&E-stained slide or grading of the proportion of stained cells, or the intensity of the staining. In light of this, the department wanted to ensure our pathologists had sufficient training and familiarity with digital IHC slide use before they started using digital IHC slides in routine practice.

6.2.1 A validation protocol for digital immunohistochemistry assessment

A digital IHC training and validation protocol was developed, which is a simplified and streamlined version of the digital primary diagnostic training and validation protocol recommended by the Royal College of Pathologists in their best practice guidance.[1] See table 26 for an overview of this protocol.

Phase	Aim	Description
1. Basic Skills	Pathologist familiarisation with digital pathology software	30-60 minute session Observed practice with feedback
2. Validation and training cases	Pathologist familiarisation with digital IHC images Identification of challenging cases Identification of IHC types that require routine 40x scanning	Pathologist views a set of approximately 10 relevant training cases covering a range of stains and scenarios Discussion and feedback
3. Ongoing surveillance	Clinical governance of digital reporting Assessment of scanning requirements for new stains/scenarios	Adhere to local/national clinical governance guidelines Consider yearly audit of IHC digital reporting

Table 26. Summary of validation protocol for immunohistochemistry assessment

6.2.1.2 Phase 1: basic skills training

The aim of this stage is to train each pathologist in the use of the digital pathology system. This stage can be truncated or omitted for pathologists who are already experienced in using the digital pathology system. It consists of a short (30 min–1 hour) training session in which the pathologist learns from an experienced user of the system (a trainer). Access to a help manual and training slides is required.

The pathologist is taught:

- The basic digital pathology workflow and layout of the software.
- How to use the system to open a case/slide and pan and zoom
- How to use the system to annotate a case and other advanced functions
- How to access the documentation for the system.
- How to identify gross scanning artefacts

The trainer observes the pathologist open and read a small number of training cases and provides feedback.

6.2.1.3 Phase 2: validation and training cases

The aim of this stage is to train the pathologist on the appearance of digital IHC slides. It includes exposure to cases anticipated to be challenging to diagnose digitally, and encompasses a variety of case types and stains as defined in the validation scope. Discussion with pathologists prior to validation can be used to identify stains and scenarios that are potentially difficult to diagnose on the digital platform or those that have important therapeutic implications for patients.

A set of slides was prepared for each subspecialty, comprising a set number of IHC cases for each specialty (this varied from 6 to 15 cases, and individual case size varied from 1 to 15 immunostains). Glass slides, digital slides and clinical information were made available to the pathologist. The cases included slides from a variety of relevant tissue types, covering a range of IHC stains and diagnostic scenarios. The cases were selected to allow the pathologist to explore specific aspects of digital IHC, which were relevant to that individual pathologist's practice and have experience of viewing a range of features on the digital microscope. As the scope of the validation protocol is to train and validate the pathologist's use of digital for IHC assessment only, and did not extend to primary diagnosis, it was felt that a relatively small validation set of cases should be prepared for each specialty, in contrast with the Royal College of Pathologists' Guidance on primary diagnostic validation case numbers[1] and the College of American Pathologist's guidelines[74] (approximately 2 months whole time equivalent caseload and a minimum of 60 cases, respectively). A typical 'case' for these purposes can consisted of a few representative slides and does not have to include all material from a complete clinical case.

The pathologists were asked to review their personalised training set, in their own time, over a short period of time (eg, up to 2 weeks). For each case, they made notes on their digital slide diagnosis. Then they immediately review the glass slides for the same case and noted their diagnosis. They were able to make comments on the case on a proforma, including their diagnostic confidence using both the digital and the glass slides for the case, expressed on a numerical Likert scale from 1 to 7 (where

1=not confident at all and 7=very confident). This allows the pathologist and trainer to distinguish between slides that the pathologist finds difficult to assess on any diagnostic medium, and slides that are particularly difficult to assess confidently on the WSI. At the end of the training set, the results were discussed at a small group training meeting. This included discussion of the pitfalls noted in the test set and explicit identification of the cases/features known to be difficult. If any particular type of stain or scenario was found to be problematic on digital slides, and this was not resolved following review of digital slides and discussion within the training group, the researcher provided more examples for training and where appropriate, offered to rescan cases at ×40 equivalent magnification.

Once the pathologist and trainer were both satisfied that the pathologist was familiar with the operation of the system and its use in the training cases, the pathologist was allowed to view and assess their IHC using digital slides as default. If any areas of diagnostic difficulty were identified, certain glass slides could be protocolled for scanning at higher magnification, or a mandatory glass check prior to case sign out could be mandated.

6.2.1.4 Phase 3: ongoing surveillance

Once a pathologist has completed their training for digital IHC reporting in a particular specialty, ongoing quality assurance procedures should be followed as part of normal departmental clinical governance procedure. Local incident reporting procedures should be adhered to, as they would for conventional

microscopic practice. Cases should be peer reviewed for multidisciplinary team meetings, and difficult/challenging cases should be shared for second opinion, or

discussed at existing intradepartmental meetings, in settings where both glass and digital images can be studied. The department should consider introducing audit protocols to allow a random review of a proportion of an individual pathologist's digital cases on a rolling basis.

6.2.2 Validation and training outcomes

A total of 24 pathologists completed the digital IHC training and validation exercise, representing 11 histopathology reporting subspecialties. The number of IHC cases viewed per specialty varied from 6 to 15 cases, and individual case size varied from 1 to 15 immunostains. A total of 1480 slides were viewed and assessed in the course of the validation by all participants. The mean satisfaction score with digital IHC slides, expressed on a Likert scale of 1–7, where 1=not at all satisfied, and 7=very satisfied, was 5.91. The range of observed responses was 2–7 (see figure 19).

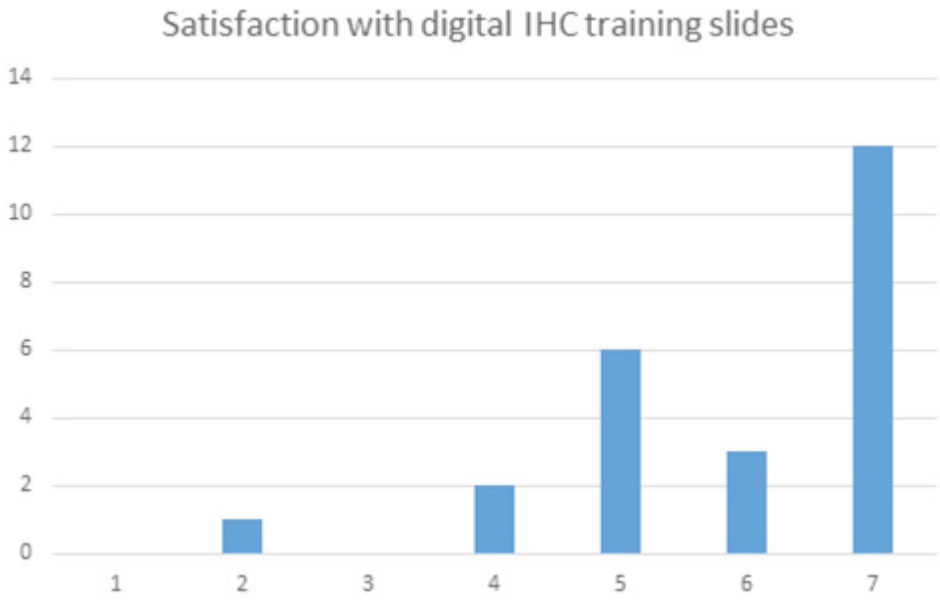

Figure 19. Pathologist reported satisfaction with digital IHC training slides. Satisfaction is reported on a Likert scale from 1-7 (x –axis), where 1 is not at all satisfied, and 7 is very satisfied indeed.

There was complete IHC assessment clinical concordance for all cases and all observers across the validation study, with no clinically significant difference in IHC interpretation observed. Across the validation, the average confidence score for digital slide IHC assessment was 6.1 (range, 2–7), compared with 6.9 (range, 6–7) for glass slides. Cases scoring low confidence values on digital slide assessment contained particular IHC stains, which pathologists almost universally reported as being difficult to assess on digital in free-text comments.

6.2.3 Free-text comments

Pathologists were encouraged to support their scoring for satisfaction with digital slides, and confidence in diagnosis on digital versus glass slides with free-text commentary. Cases scoring high confidence marks on digital slides (6 or 7), and pathologists rating their satisfaction with digital slides as high (6 or 7) gave the following feedback:

- *Found digital as quick and as easy as the glass slide.*
- *Found it easier to spot areas of concern at low power on the digital slides than on glass.*
- *Positive results are spotted more quickly on the digital slide.*
- *I find it easier to assess a multislide case digitally. I can see all the IHC requested at one glance, then quickly zoom in to check staining pattern.*
- *Easy to use and interpret.*
- *Quicker looking at digital images.*
- *Digital IHC seems more crisp.*

Cases scoring low confidence marks on the digital slides anything below 6) and pathologists rating their satisfaction with digital slides as low (anything below 6) provided the following feedback:

- *Screening large volumes of tissue for rare positive cells gave me a headache.*
- *It took me longer to scroll through all the tissue at high power than on my light microscope.*
- *Need higher magnification scanning for some stains.*
- *Helicobacter pylori blurry and difficult to spot.*

In addition, the pathologists identified a number of immunostains that they found difficult to interpret with confidence using standard images captured at ×20 equivalent magnification. These immunostains belong to a category of stains that either require some form of advanced assessment (eg, quantification, complex location) and/or would have direct therapeutic implications for the patient (eg, decision to offer or not offer a drug therapy). See table 27 for a list of these stains.

Stain	Rationale
Her2	Requires quantification of intensity and volume Therapeutic relevance
ER, PR for breast and gynaecological tumours	Requires quantification of intensity and volume Therapeutic relevance
Helicobacter pylori	Requires tissue search for small, sometimes sparse diagnostic objects
Ki67	Requires quantification, can be key part of tumour grading and hence prognosis and therapeutic management
Sv40	Difficult to locate and localise in renal biopsies
CMV	Difficult to locate and localise in renal biopsies

Table 27. Immunohistochemical stains pathologists identified as difficult to interpret at 20x magnification

Scanning this selection of immunostained slides at ×40 equivalent magnification improved the ability of our pathologists to make a confident diagnosis, and direct comparison of ×20 and ×40 captured images demonstrated appreciable difference in the appearance of the slides. As a result of this, these slides are now mandated for ×40 equivalent scanning, while the remainder of the IHC workload is scanned at ×20. Pathologists can request repeat scanning at ×40 of any immunostained slide which they are not confident to assess at ×20, following initial ×20 assessment.

6.2.4 Conclusions

This study demonstrated complete concordance of WSI and glass slide assessment of IHC using digital images capture at ×20 equivalent magnification. While this is reassuring, it is important to consider the pathologist's confidence in their WSI assessment, and the efficiency and ease with which the diagnosis is rendered too. The majority of pathologists were satisfied and confident to use digital IHC slides rather than glass slides to report live cases, but they did highlight individual immunostains and diagnostic scenarios that were difficult to assess on standard ×20 captured WSI. The approach highlighted the need for careful assessment of a digital pathology system and scanning protocols before pathologists are expected to transfer from the light microscope to the digital microscope for routine IHC assessment. A small number of immunostains requiring more sophisticated assessment in terms of localisation and quantification of staining were problematic for our pathologists, who were unable to reach a confident diagnosis. For these cases, routine scanning at ×40 was beneficial.

The assessment of IHC is becoming an increasingly complex and time-consuming process, as more diagnostically and therapeutically useful antigens are identified and incorporated into the workload of the clinical pathologist. Pathology services are under increasing pressure to provide detailed, accurate IHC assessments within short turn-around-times (TAT), at a time when many institutions are suffering from a shortage of pathologists. The judicious development and use of artificial or augmented intelligence to read and interpret IHC stained slides could provide diagnostic support to the 21st-century pathologist, allowing them to concentrate on the morphology, while algorithms locate and quantify immunopositive regions of IHC slides.

6.3 Conclusion

The fundamental principles of the digital pathology validation protocol outlined in chapter 4 can adapted to scenarios beyond primary diagnostics. The core principles of selection of evidence based training targets, individualisation at the level of the pathologist, and consolidation of learning and experience through direct comparison of digital and glass slides are retained, whilst the protocol is truncated to reflect the relatively narrow scope, and lower risk of the clinical scenario considered (IHC or frozen section assessment).

Chapter 7. Maintaining quality and safety with digital diagnosis

This chapter summarises work by the author from the following publications:

Williams BJ, Knowles C, Treanor D
Maintaining quality diagnosis with digital pathology: a practical guide to ISO 15189 accreditation
***Journal of Clinical Pathology* 2019;72:663-668.**

Williams BJ, Treanor D
Practical guide to training and validation for primary diagnosis with digital pathology
***Journal of Clinical Pathology* Published Online First: 29 November 2019**
doi: 10.1136/jclinpath-2019-206319

Williams B, Hanby A, Millican-Slater R, Verghese E, Nijhawan A, Wilson I, Besusparis J, Clark D, Snead D, Rakha E, Treanor D.
Digital pathology for primary diagnosis of screen-detected breast lesions – experimental data, validation and experience from 4 centres. Accepted for publication February 2020, *Histopathology*.

Interest in the deployment of clinical digital pathology systems for primary diagnosis has increased dramatically in the timeframe of this body of work, fuelled by the evolution of hardware and software solutions on the market, and the need for pathology services to tackle ever-increasing workloads, with a dwindling workforce, while maintaining quality and timeliness of diagnosis.[27] Many departments have either deployed scanning technology or have planned or initiated a deployment, to harness the flexibility of digital images and potentially improve service capabilities. In this chapter, three key areas pertaining to safety and acceptability of clinical digital pathology services will be discussed – ISO accreditation, detailed guidance on digital pathology training, and the use of WSI in the UK cancer screening programmes.

7.1 ISO accreditation for digital pathology services

'ISO 15189 Medical laboratories—Requirements for quality and competence' is an international standard that specifies the quality management system requirements pertinent to medical laboratories.[86]Successful laboratory accreditation with national bodies (including UKAS in the UK, CLIA in the USA and SWEDAC in Sweden) should reassure patients and clinicians that the staff who carry out diagnostic and prognostic tests are competent, and that the equipment and processes they use are safe and fit for purpose. The deployment and integration of digital pathology diagnostic systems in a clinical histopathology department represents a departure from standard laboratory procedures, and the scope of accreditation will have to include examination of hardware and software, calibration of tools and devices, and the training and competence of laboratory staff and diagnosticians.

In order to prepare for the Leeds Teaching Hospitals ISO inspection of digital pathology output in Summer 2018, procedures and documentation had to be presented to a team of inspectors to demonstrate measures taken to ensure safety and reliability in the laboratory and the diagnostic office. At this time, there was no formal guidance available for pathology departments on the specific types of evidence required for successful digital pathology accreditation. This could be a key barrier to implementation for many clinical departments, as planning for an inspection is a time consuming process. Preparation for accreditation inspection always requires effort and exertion on the part of the laboratory. The novelty of digital pathology, and laboratories' relative inexperience using it, can make the process even more daunting. Stress can be minimised by careful planning in the early stages of a deployment, so the groundwork can be layed for safe, responsible

practice from day one. Our preparations at Leeds resulted in successful UKAS accreditation of primary digital diagnosis in our department. Details of the approach developed with the assistance of Chloe Knowles, biomedical scientist have been disseminated and published to aid other departments in their inspections. [87]

7.1.1 General principles of UKAS inspection

The first formal assessment for accreditation is an 'initial assessment', conducted by a Lead Assessor supported by technical assessors able to cover the scope of the application (including digital pathology).[88] The assessment involves detailed review of relevant departmental records, interviews with staff and managers and the witnessing of key activities, which may include digital diagnosis and slide scanning. It is important to identify key individuals, both in the laboratory, and among pathology diagnostic staff who will take responsibility for the delivery of core aspects of the accreditation procedure, and keep regular track of progress.

7.1.2 Laboratory considerations

ISO 15189 requires validation (assurance that a system meets the needs of stakeholders) and verification (evaluation of whether a system complies with regulation, requirement and specification) for any new process or technique that has been implemented in a laboratory. For digital pathology deployment, assessors will need to view a written document, supplemented with evidence, which addresses a number of key aspects of the implementation:

- Change control
- Risk assessment

- Verification and acceptance
- Comparability and reproducibility
- Training and competency
- Uncertainty of measurement

7.1.3 Change control

Change control, the systematic management of all changes to a system or process, is a vital part of a digital pathology deployment, and ensures that all changes are documented, no unnecessary changes are made, resources are utilised efficiently and existing services are not unnecessarily disrupted. A full change control procedure, complete with documentation, must be developed and adhered to if digital pathology is being implemented into the laboratory as a new process. It is essential for ISO 15189 and ensures all aspects of the implementation are assessed and managed appropriately. It allows key people to be identified to ensure appropriate stakeholder engagement and that all evidence is submitted correctly and in a timely manner. If an initial accreditation inspection raises findings that need to be addressed or resolved prior to the next assessment, it also simplifies the process of resubmitting evidence. Key personnel to engage during the change control process might include the clinical lead, representatives of departmental management (business, operations and service), the departmental health and safety officer, quality control manager, members of laboratory staff of all grades, and a change lead.

7.1.4 Risk assessment

The health and safety risks of the proposed digital pathology process need to be scoped and assessed before it can be implemented. The departmental health and safety representative will be an invaluable resource to advise and assist in carrying out risk assessments. Types of assessment include:

- Equipment usage (scanners, computer workstations etc).
- Proposed processes and workflows
- A general risk assessment to include the environment in which the equipment will be sited, and how the laboratory staff will work safely the equipment.
- New screen display assessments for all staff will be using new screens either in the laboratory or the diagnostic office.

7.1.5 Verification and acceptance

Verification for ISO 15189 in the laboratory requires evidence to show that the scanners and software have been adequately tested for their intended use, and are working as required, and as the manufacturer states. This includes the scanners, any software provided by the company and any databases used. A written document detailing the evaluation methods and results must be submitted as evidence. A good way of providing this is to run internal tests against the initial manufacturer's installation and verification checklist from when the scanners were first installed.

7.1.6 Comparability and reproducibility

If multiple scanners are being utilised as part of the digital pathology system, ISO 15189 requires evidence to demonstrate that all scanners used produce images that

are of equal diagnostic quality. This can be done by scanning a test set of slides on each of the scanners and asking a suitably experienced and validated digital pathologist to assess them. Suitable cases might include a malignant breast core biopsy for tumour grading, a bowel cancer screening specimen and a sentinel lymph node.

Factors to consider when assessing the images would be:

- Is the background clear?
- Is the image in focus?
- Is the staining crisp and clear?
- Are the images comparable across all scanners?
- Is there a significant difference in the interpretation of key diagnostic features in images obtained from different scanners?

Inter-laboratory assessment schemes are common for standard glass slide histology, and are likely to be adopted for digital pathology whole slide images too. This would involve departments exchanging whole slide images, and asking pathologists to assess images produced in different laboratories. As digital pathology is a new technique, it may be difficult to share images from one department to another. An alternative to an inter-laboratory scheme is to rescan a case previously scanned and ask the reporting pathologist to reassess the case and compare their assessment with the original report.

7.1.7 Training and competency

All parts of the digital pathology process need formal documentation in the form of quality managed standard operating procedures (SOPs). Laboratory staff should be familiar with these documents, and able to access them easily for reference.

Examples of SOPs include the following:

- How to operate the scanners.
- How to operate the image software and database.
- Troubleshooting—both for the scanners and workflow.
- Maintenance of the scanners.

To complement the content of the SOPs, relevant training booklets and competency assessments need to be documented and regularly reviewed. To ensure staff feel safe to work in digital pathology without supervision, a suitable training programme should be delivered to all new users of digital pathology in the laboratory. These SOPs and training materials will require regular updates to reflect changes in practice and the acquisition of new and updated hardware and software.

7.1.7 Uncertainty of measurement

If digital measurement software is being utilised as part of clinical diagnosis, one needs to tackle the question of uncertainty of measurement. A calibration slide with predefined values can be used to assess whether scanned objects are captured to scale, and this should be audited within the department. An example of a calibration slide (Applied Image, NY, USA) is shown in figure 20. It contains a marked area with a predetermined height and width, with expected measurement given by supplier's calibration data. Suppliers should provide a calibration certificate with this slide. A width and height measurement should be recorded using the proposed clinical measurement tool and monitored for any changes that are deemed out of the

reference range. Scanner suppliers will differ in their approach, but is important to check the scanner's documentation to determine the reference ranges the measurements can fall under, for example, ±0.15 mm. This process should be repeated for all scanners used to scan slides for primary digital diagnosis, and any measurements falling outside of the manufacturer's acceptable reference range should be reported. As with any other equipment used for measurement in a medical laboratory, the calibration slide itself needs to be calibrated. The process and frequency of this will differ between suppliers, so it is important to check how often this should be done.

To satisfy a clinical department, and an accreditation assessor that digital measurements taken on WSIs using slide viewing software are safe for clinical use, one needs to demonstrate that measurements taken on diagnostic images are accurate and reproducible. A relatively simple approach to this is to carry out and document an audit of clinically relevant measurements appropriate for the scope of the intended digital diagnostic practice. A small set of glass slides encompassing tumour measurements/margin assessment/tumour thickness, etc, can be assembled, and pathologists can be asked to make repeat measurements on glass and digital once a day for week or two. In this way, variability in measurement on both glass and digital slides can be documented, using both inter-observer and intra-observer comparisons.

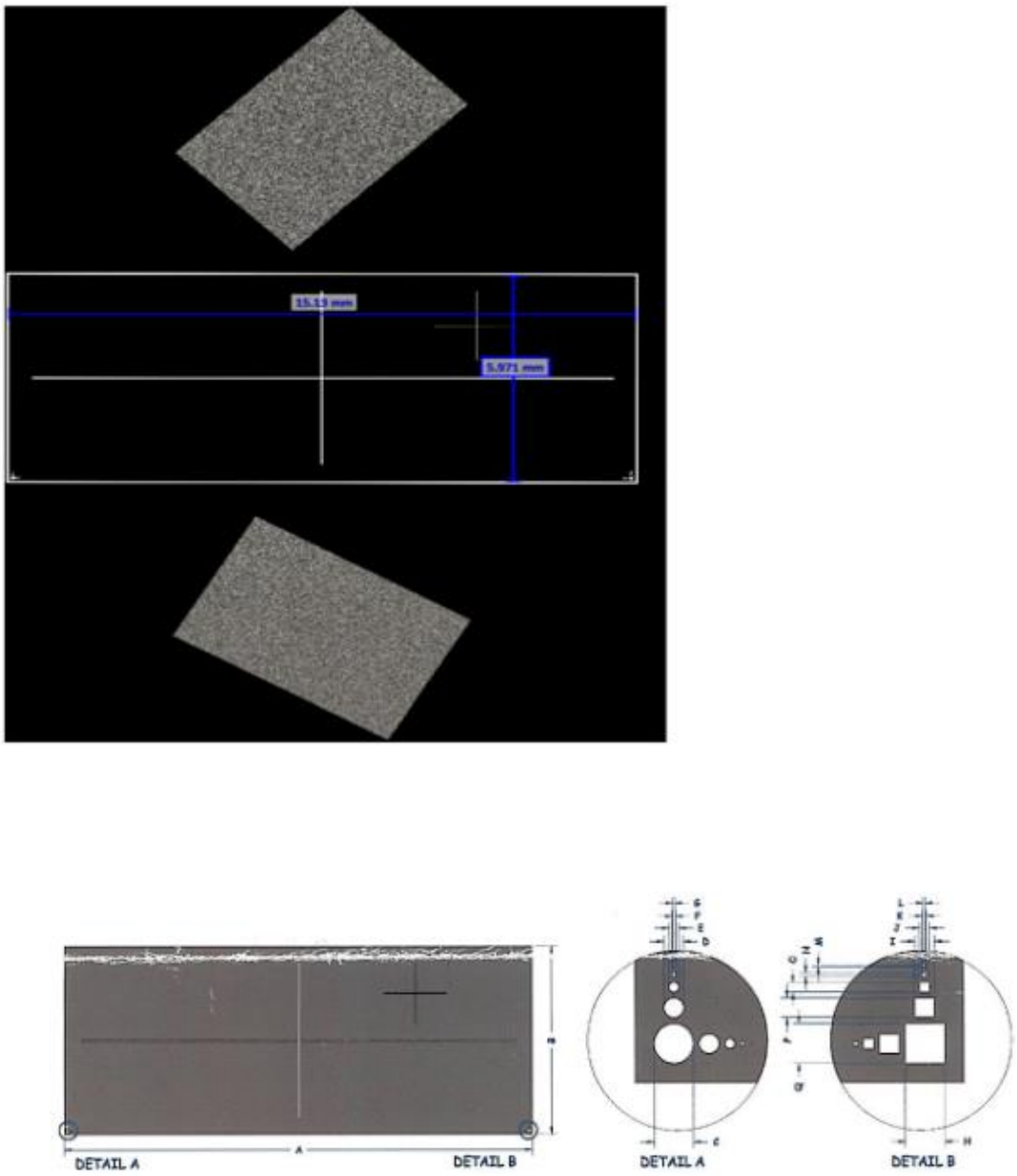

Figure 20. An example of a commercially available calibration slide from Applied Image, NY, USA. The slide contains objects of known dimensions, which can be measured and compared with certified measurements made by the manufacturer.

7.1.8 Post-accreditation monitoring

At this point in time, based on the Leeds Teaching Hospitals experience of digital pathology implementation, and existing national benchmark frequencies (eg, annual

External Quality Assurance schemes, annual appraisal), yearly audit/quality assurance benchmarks for digital pathology systems would seem advisable. As experience in digital pathology accumulates, and it becomes standard practice, the need for audit may reduce, as pre-existing departmental accuracy audits will simply be performed on digital slides as standard.

7.2 Clinical and diagnostic considerations

All the SOPs and workflows established in a laboratory should ensure that diagnosticians are presented with quality whole slide images in a safe and timely manner. This rigour needs to be matched with appropriate training and validation in the diagnostic office.

7.2.1 Validation and training

Meaningful digital diagnosis training and validation should result in:

- Pathologists that are confident in their abilities and their limitations with digital diagnosis.
- Pathologists that are familiar with their hardware and software, and can recognise and report performance issues
- A department with a shared understanding and investment in the digital pathology system
- A department that can develop bespoke ways of using digital to improve its outputs, workflows and working environment

7.2.2 Preparing clinical pathologists for accreditation

Consultants should have ready access to their own data, documenting their individual training and validation for digital reporting, copies of relevant SOPs and protocols, and user guides/manuals for the software they use. A specific personal folder containing this information for each consultant could be stored on a shared departmental drive, and accessed via a desktop shortcut.

Each pathologist should be able to demonstrate how they report a case to the assessor, and how they would recognise and report issues with digital slides, such as out of focus regions or digital artefact. Depending on local departmental SOPs, technicians may protocolise reflex rescanning of inadequate slides (digital slides on which the pathologist is not prepared to make a diagnosis for quality reasons), or deferral to glass slides in this situation. All quality issues should be reported and fed back to the laboratory, regardless of whether the pathologist can make a diagnosis or not on the suboptimal slide. Examples of suboptimal slides are presented in figure 21.

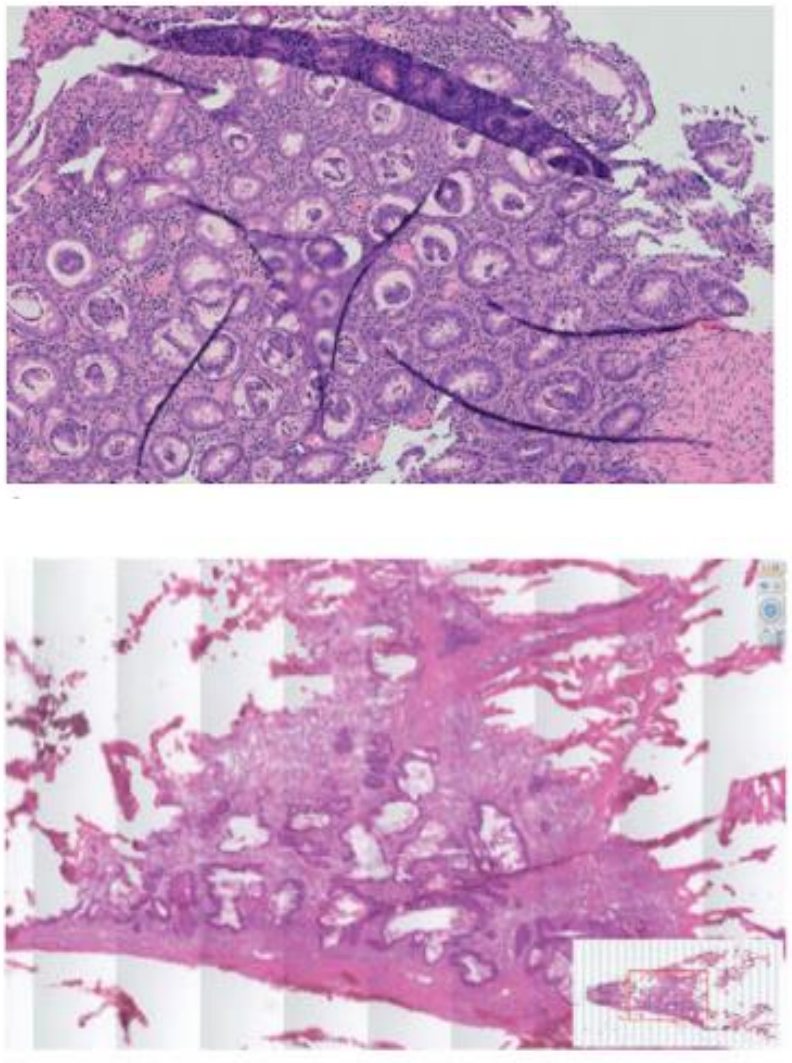

Figure 21. Examples of suboptimal digital slides. In each case, the pathologist would need to exercise their judgement in deciding whether the artefact precludes safe diagnosis. Top – Tissue folding in the original glass slide is replicated in the digital slide. Bottom – "Striping" artefact introduced during scanning.

Pathologists that are reporting digitally should be familiar with, and able to access departmental SOPs for digital slide reporting, training and validation in digital reporting, and the relevant user guides for the software/slide viewer they use for primary diagnosis. They should be able to access their individual validation documentation, and talk through the implications of this validation, describing any situations in which they would defer to glass slide reporting. It can be helpful to circulate spreadsheets/templates for pathologist to record data on cases where they

need to defer to glass, or where digital slides are suboptimal for assessment, which can be fed back to the laboratory on a regular basis.

7.2.4 Post-accreditation monitoring

Accreditation is an ongoing process, and departments must continuously monitor, and strive to improve the quality and safety of their digital pathology service. In light of this, it is important to continue to audit and evaluate digital diagnosis after successful ISO accreditation. This should include documentation and investigation of scanning issues (eg, out of focus slides/ slide regions, incidence of digital artefact) and diagnostic issues (eg, frequency and reason for deferral to glass). Digital diagnosis can be audited on an annual or 6 monthly basis, by retrieving a random sample of archived cases, and reviewing the diagnosis. This could incorporate comparison with glass slides, providing the pathologist participating in the audit with an opportunity for continuing professional development.

7.2.5 **Training points for primary digital diagnosis**

Experience from Leeds Teaching Hospitals NHS Trust deployment, and the pilot validations detailed in chapters 5 and 6 has identified a number of key areas where novice digital pathologists can experience difficulty. Diagnosis of all types of case is possible on the digital microscope, but confident and efficient sign out of all cases will take time and experience. ‘Safety nets’ such as the use of adjunct immunohistochemistry or glass slide deferral in particular circumstances or for particular types of case can be used and should not be viewed as ‘failure’ of the digital

system. As pathologists' digital reporting experience grow, they will find that the proportion of cases they are comfortable to sign out increases. While relatively little is known about what the minimum specification should be for a digital pathology workstation for primary diagnosis, use of quality, high resolution screens can improve pathologists' ability to assess some of the more challenging cases and features described below.

7.2.5.1 Detection of small diagnostic and prognostic objects

The smooth and efficient navigation of digital cases, both between slides in a multislide case and within a slide that requires a high magnification search can be problematic. The initial low magnification, whole slide image displayed on the computer screen can provide a fantastic 'spot diagnosis' of a predominantly architecture-based diagnosis, for example, adenomatous polyp, fibroadenoma, but it can also provide false reassurance. One of the most common diagnostic discordances that can occur when a novice starts digital diagnostic training is missing a small diagnostic or prognostic object. [89] Examples of this include missing a metastasis or micrometastasis in a sentinel lymph node case (see figure 22) or failing to identify a single focus of cryptitis in a multislide colonic biopsy series. It is vitally important that pathologists have sufficient time to adapt and develop their own navigation strategies on the digital microscope. The tried and tested 'lawnmower' technique to ensure complete high power coverage of a slide on the light microscope is difficult to replicate on the digital microscope. Judicious use of whole slide and whole case thumbnails can aid navigation of a digital case, and

features such as indicators that warn pathologists of missed slides/regions of slides can help, particularly in the early stages of digital training.

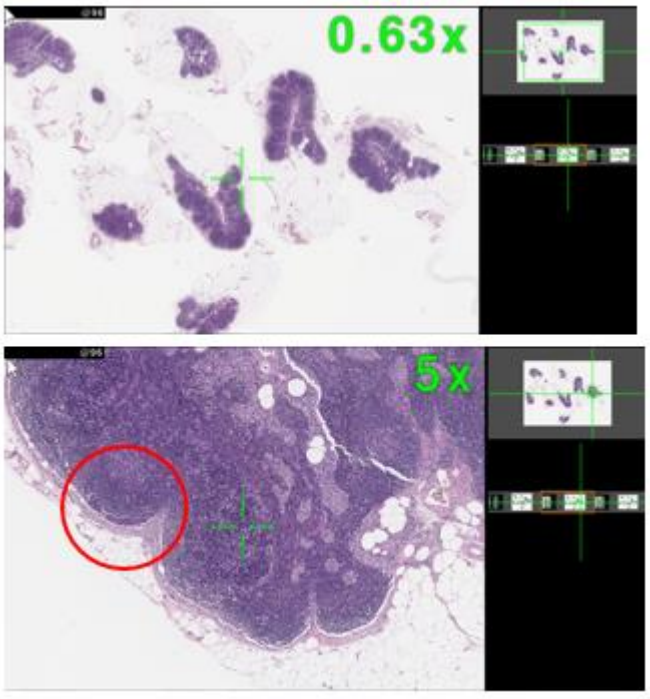

Figure 22. Assessment of a sentinel lymph node on the digital microscope. A pathologist might be reassured by the benign appearance of the extreme low power view (top image) but zooming in to just 5x equivalent magnification reveals a micrometastasis which would have affected patient management.

7.5.2.2 Dysplasia

The diagnosis and grading of dysplasia on the digital microscope is a recurrent theme in the WSI discordance literature and is a potential pitfall for the new digital pathologist. There are two areas of concern here: diagnostic issues at 'low power' and 'high power'. Discordance can result from a failure to detect a focal region of dysplasia on the initial low power assessment of epithelium (eg, in a cervical biopsy). This type of problem is discussed above. The other issue implicated in the misdiagnosis/grading of digital dysplasia relates to the rendering of nuclear detail on digital scans, with some authors implicating poor focus, exacerbated by compression

artefact and the limited dynamic range of the WSI[58]. There is a definite learning curve for digital dysplasia assessment, and a validation procedure involving direct comparison of a pathologists digital and glass assessment of dysplasia cases can help the pathologist reconcile their digital and glass dysplasia identification and grading. Routine use of 40× scans for diagnostic biopsies and a high contrast, high resolution, medical grade display can also improve confidence in diagnosis of tricky or borderline cases.

7.5.2.3 Mitotic figure counting

Accurate identification and counting of mitoses is another recurrent theme in the digital pathology discordance literature. [61,62,73,79] In the absence of z-stacking, pathologists have to rely on an image captured at a single best plane of focus and cannot adjust this to focus through the depth of the nucleus for chromatin assessment.

Similarly to assessment of dysplasia, there is a learning curve for digital mitotic counting. In cases of uncertainty, where the mitotic count on digital is at a critical cut-off level, which would affect overall grading and treatment for a patient, a confirmatory glass slide check should be encouraged. Mitotic counting is an area where artificial intelligence and computer assisted diagnosis could assist the digital pathologist in the near future.

7.5.2.4 Specific diagnostic items and features

Examination of the literature[89] highlights a number of diagnostic/ prognostic items and features which may have a subtly different appearance on a WSI. Many of these

items share common features: they are often eosinophilic, refractile entities. Other items of particular note include the weddelite form of calcification in breast biopsy specimens and amyloid. Both entities can be viewed on standard WSI images, but experience from validation studies suggests that there is a learning curve for confident recognition on the digital slide.

7.5.2.5 Potential pitfalls

Table 28 summarises some of the potential pitfalls of digital diagnosis in different diagnostic subspecialties, as evidenced by the validation literature and practical experience of validation. These potential pitfalls should form the basis of digital primary diagnostic training.

Histopathology subspecialty	Potential pitfalls
General [89]	Identification and grading of dysplasia Identification of lymph node metastasis and micrometastasis Identification and quantification of mitotic figures Identification of granulation tissue Identification of micro-organisms
Breast [38,43,56,60,80,85]	Identification and grading of nuclear atypia Identifying microinvasion and lymphovascular space invasion Identification of lobular carcinoma Grading invasive cancers (mitotic count component) Identification of weddelite calcification Identification of sentinel lymph node metastasis/micrometastasis
Skin and soft tissue [51,55,70,89]	Identification and grading of squamous dysplasia Micro-organism detection Granulomatous inflammation Melanocytic lesions Granulocyte identification and classification

	Identification of sentinel node metastasis Identification of amyloid Identification of lymphoproliferative disease/malignancy
Endocrine[89]	Identification of granulomata Identification of lymph node metastasis Identification of amyloid in medullary carcinoma of the thyroid Classification of thyroid neoplasms- identification of cellular papillary features Identification of mitoses and atypical mitoses
Genitourinary[52,59,62,66,69]	Identification and grading of urothelial dysplasia Identification of micro-organisms Identification of granulomatous inflammation Identification and classification of inflammatory cells (especially granulocytes) Identification of amyloid Identification of lymphoproliferative disease/malignancy Grading renal carcinoma (nuclear features)
Gastro-intestinal[54,58,62,64,65,67]	Identification and grading of oesophageal dysplasia Identification of focal activity in inflammatory bowel disease Identification of eosinophils in oesophageal biopsies Identification of granulomata Identification of micro-organisms – particularly Helicobacter pylori
Gynaecological [68,89]	Identifying and grading cervical dysplasia Identifying metastasis/micrometastasis Assessing endometrial atypia Identifying mitotic figures (particularly in soft tissue uterine lesions Identifying mucin
Head and neck [89]	Identification and grading of squamous dysplasia Identification of micro-organisms including fungal forms Identification of granulomata Identification and typing of inflammatory cells
Hepatobiliary/pancreatic [89]	Interpretation of liver special stains

	Identification of dysplastic epithelium (particularly gall bladder) Identification and typing of inflammatory cells Identification of granulomata
Cardiothoracic [89]	Identification of dysplasia/malignancy in small biopsy specimens Identification of micro-organisms including mycobacteria Identification of granulomatous inflammation Identification of micrometastasis in EBUS specimens

Table 28. Potential pitfalls of digital diagnosis organized by topography

7.2.6 Continuing surveillance and audit

Following introduction of digital primary diagnosis, data should be collected routinely on:

- frequency and root cause of poor quality/out of focus/artefact containing WSI
- frequency and details of instances when pathologists defer to glass slides.

WSI diagnosis can be audited in a similar way to existing departmental glass slide diagnostic audit, with a random sample representing a proportion of the diagnostic workload reviewed by a second pathologist.

7.2.7 Conclusion

The body of work detailed in this thesis has formed the basis of a practical guide to advise clinical histopathology departments on how to train and validate their pathologists for primary digital diagnosis, which summarises the key steps and considerations and provides a detailed list of evidence-based 'potential pitfalls' and training targets for digital reporting. Digital pathology technology and our

appreciation of the scope and limitations of digital practice continue to evolve, and with this in mind, it is important that the pathology community continues to prioritise the quality and safety of our diagnosis with the introduction of new technologies and techniques.

7.3 Digital pathology and patient safety for cancer screening programmes

In clinical pathology, breast pathologists are experiencing increasing pressure in terms of breast cancer case volume, case complexity, and the need for rapid evaluation and review to meet cancer diagnostic and therapeutic targets. Within this, one of the most challenging areas facing the NHS breast screening programme (NHSBSP) is the identification of pre-cancers, atypia, and early stage cancers. This area involves the identification of subtler morphologies, and the increasing use of adjunctive immunohistochemistry. Digitisation of slides could be of benefit to the NHSBSP, allowing more streamlined distribution of screening cases to pathologists, and faster access to archived cases for comparison, but also must be able to accurately classify the atypias and other borderline lesions of potential significance.

Interest in the use of DP for the primary diagnosis of histological specimens is flourishing, with a number of laboratories using digital images for primary diagnosis in at least a proportion of cases. For DP to be accepted and adopted on a large scale, regulatory bodies, diagnostic departments, and individual pathologists will have to be convinced that a diagnosis made by a particular pathologist on a digital microscope is non-inferior to a diagnosis made by the same pathologist on a

conventional light microscope, and that no systematic error is introduced into the diagnostic process as a result of the technology.

The UK Royal College of Pathologists has published guidelines supporting the use of DP for primary diagnosis by pathologists who have received adequate training and validated their DP diagnosis[1], but at present, Public Health England (PHE), which is responsible for the NHSBSP, does not allow the use of digital slides for the primary diagnosis of screening programme specimens.

In this chapter, the results of a comprehensive review of the literature regarding DP safety are presented, particularly in the context of breast histopathology, and new concordance data from four European centres comparing conventional light microscopy diagnosis with DP diagnosis is presented. In addition, 3 types of complementary data are presented in order to provide the reader with a comprehensive overview of digital breast cancer diagnosis: (1) experimental diagnostic concordance data, (2) direct comparison diagnostic validation data and (3) experimental intraobserver variation data.

7.3.1. Experimental data

To provide a comprehensive assessment of digital primary diagnosis for breast specimens, data were collated from 3 types of experiments performed across the contributing institutions. The complementary data from these are described separately below.

7.3.1.1 Experimental concordance data

7.3.1.1.1 Aim

To establish if digital slides are diagnostically equivalent to the glass slides they represent.

7.3.1.1.2 Materials and methods

The study was performed in the histopathology departments of University Hospitals Coventry, and the Centre for Pathology, Vilnius, Lithuania. Fully qualified consultant histopathologists with specialist experience reporting breast specimens were recruited to participate. Each centre utilised their own departmental digital pathology hardware and scanning protocols, detailed in table 29.

	University Hospitals Coventry	Centre for Pathology, Vilnius
Scanning hardware	Omnyx	Leica Aperio Scanscope
Scanning magnification	40x	20x
Viewing hardware	DELL standard desktop screen, non medical grade, 1920p x 1080p resolution	DELL standard desktop screen, non medical grade, 1920p x 1080p resolution
Viewing software	Omnyx VL4	Aperio ImageScope
Number of consultant participants	2	1

Table 29. Digital pathology scanning and viewing specifications – experimental data.

Complete breast pathology cases, including immunohistochemistry and special stains where applicable, were selected from departmental archives and scanned. participants viewed digital breast pathology cases and recorded their diagnoses, as they would in their routine practice. These diagnoses were then compared with

archived light microscopy reports for the same cases. In cases of disagreement of discordance, both glass slides and digital slides were reviewed by an expert consensus panel to establish ground truth. A discordance was classified as any material difference in the diagnosis, regardless of whether this would have affected patient prognosis or treatment. Full details of each discordance were recorded, but discordances were not classified as minor or major, to reflect differences in practice in the different centres.

7.3.1.1.3 Results

Pathologists at the 2 sites viewed a total of 475 complete breast pathology cases. (View table 30 for a breakdown of the data by site).

	University Hospitals Coventry	Centre for Pathology, Vilnius	Combined results for both sites
Number of cases	250	225	475
Complete concordance	249	216	465
Discordances	1	9	10
Concordance rate (%)	99.6	96.0	98.7

Table 30. Experimental digital pathology versus light microscopy concordance data.

The clinical concordance rate for combined data across both sites was 98.7%. Only 10 clinically significant discordances were observed, the majority of which were differences in invasive tumour grading attributable to differences in mitotic count scoring. (See table 31 for a detailed list of discordances, and the corresponding diagnostic B-codes.) Please refer to table 32 for a description of National Health Service B codes. These are alphanumeric codes used to categorise breast biopsy

diagnoses, and correspond to different management options. A difference between B codes e. g B2 versus B5a, could result in differences in further management of a patient, whilst a difference in tumour type (lobular versus ductal carcinoma) or grade (2 versus 3) would not lead to differences in further management, as it is likely the correct diagnosis would be appreciated in the resection specimen.

Digital diagnosis	Digital diagnostic B code	Glass slide diagnosis	Glass slide diagnostic B code	Ground truth
Grade 2 IDC	B5b	Grade 3 IDC	B5b	Glass
Grade 2 IDC	B5b	Grade 3 IDC	B5b	Glass
Grade 1 IDC	B5b	Grade 2 IDC	B5b	Glass
Grade 1 IDC	B5b	Grade 2 IDC	B5b	Glass
Hamartoma	B2	Adenosis	B2	Glass
Grade 2 IDC	B5b	Grade 1 IDC	B5b	Glass
Grade 2 IDC	B5b	Grade 1 IDC	B5b	Glass
Grade 1 ILC	B5b	Grade 2 ILC	B5b	Glass
Normal lymph node	N/A	Reactive lymph node	N/A	Glass
Grade 1 IDC	B5b	Grade 2 invasive ductal carcinoma	B5b	Glass

Table 31. Experimental discordances encountered

Breast biopsy diagnostic B code	Description
B1	Normal
B2	Benign
B3	Uncertain malignant potential
B4	Suspicious
B5a	Malignant in situ
B5b	Malignant invasive
B5c	Malignant not assessable

Table 32. Diagnostic B codes for breast biopsy specimens (NHS, UK)

7.3.2 Direct comparison validation data

7.3.2.1 Aim

To train and validate individual pathologists for the primary digital diagnosis of breast pathology using a direct comparison method endorsed by the Royal College of Pathologists, and evaluate clinical concordance rates throughout the validation process.

7.3.2.2 Materials and methods

The study was performed in the histopathology departments of Leeds Teaching Hospitals NHS Trust, and United Lincolnshire Hospitals NHS Trust. Five fully qualified histopathologists with specialist experience reporting breast specimens were recruited to participate. Each centre utilised their own departmental digital pathology hardware and scanning protocols, detailed in table 33.

	Leeds Teaching Hospitals NHS Trust	United Lincolnshire Hospitals NHS Trust
Scanning hardware	Leica Aperio AT2 and CS2	Omnyx VL120
Scanning magnification	40x	40x
Viewing hardware	Barco 6MP medical grade	Not specified
Viewing software	Leeds Virtual Microscope (LVM)	Omnyx VL4
Number of consultant participants	4	1

Table 33. Digital pathology scanning and viewing specifications – validation data

All pathologists followed the validation protocol for primary digital diagnosis described in chapter 4. The “live” breast histopathology work of all participating consultants was scanned prospectively, in accordance with the V2, live validation phase of the protocol. All cases were viewed digitally in the first instance, and consultants recorded their diagnosis in a spreadsheet. The corresponding glass slides

for the case were then viewed, and any difference in diagnostic opinion recorded before final sign out of the case.

7.3.2.3 Results

During their "live" validation phase, pathologists at the 2 sites viewed a total of 1077 complete breast pathology cases. (View table 34 for a breakdown of the data by site).

	Leeds Teaching Hospitals NHS Trust	United Lincolnshire Hospitals NHS Trust	Combined results for both sites
Number of cases	896	181	1077
Number of readers	4	1	5
Complete concordance	887	180	1067
Discordances	9	1	10
Concordance rate (%)	99.0	99.4	99.1

Table 34. Direct comparison digital pathology versus light microscopy validation data.

The clinical concordance rate for combined data across both sites was 99.1%. Only 10 clinically significant discordances were observed, the majority of which were differences in invasive tumour grading attributable to differences in mitotic count scoring and the detection of small diagnostic objects (eg. isolated tumour cells in a sentinel lymph node). (See table 35 for a detailed list of discordances, and table 33 for a reminder of B codes).

Digital diagnosis	Digital diagnostic category	Glass slide diagnosis	Glass slide diagnostic category	Ground truth
Grade 2 IDC	B5b	Grade 3 IDC	B5b	Glass
Grade 2 IDC	B5b	Grade 3 IDC	B5b	Glass
Benign phyllodes tumour	B3	Fibroadenoma with inflammation	B2	Glass
Benign breast tissue	B2	Atypical intraductal proliferation	B3	Glass
Sclerosing adenosis	B2	Sclerosing adenosis, small focus DCIS	B5a	Glass
Microcysts	B2	Microcysts and weddelite	B2	Glass
Benign lymph node	LB2	Isolated tumour cells	LB5	Glass
Columnar cell change	B2	Grade 2 ILC	B5b	Glass
Normal lymph node	LB2	Reactive lymph node	LB2	Glass
Small focus DCIS	B5a	No DCIS	B2	Digital
Grade 2 IDC	B5b	Grade 3 IDC	B5b	Glass

Table 35. Discordances from direct comparison validation data

7.3.3 Breast cancer screening intraobserver variation study

7.3.3.1 Materials and methods

The study was performed in the histopathology department of Leeds Teaching Hospitals NHS Trust. Fifty anonymised breast biopsy screening specimens were selected from the archive of the Department of Histopathology, St James' University Hospital. Diagnostically challenging B2, B3 and B5a specimens were selected, allowing the study to focus on the ability to categorise borderline lesions on the ductal atypia spectrum. All slides were scanned using the same Leica AT2 scanner, and viewed with Leeds Virtual Microscope viewing software. A single representative slide was selected for each case. Three consultant breast histopathologists were

recruited. Each pathologist viewed each case on four separate occasions, twice using conventional glass slides, and twice using digital slides. Participants were asked to interpret each slide as they would in their normal clinical practice, and to complete a diagnostic proforma adapted from the NHS Breast Screening Programme for each case. A washout period of two weeks was observed between slide reads of the same case. (See slide viewing schedule in table 36).

Pathologist	Read 1	Read 2	Read 3	Read 4
A	Glass slide	Digital slide	Glass slide	Digital slide
B	Digital slide	Glass slide	Digital slide	Glass slide
C	Glass slide	Digital slide	Glass slide	Digital slide

Table 36. Pathologist slide viewing schedule for breast cancer screening study.

In accordance with this schedule, each pathologist reviewed the same fifty cases four times: twice on the light microscope, and twice on the digital microscope giving a total of two hundred viewings and diagnoses each, and six hundred slide viewings and diagnoses over all.

7.3.3.2 Results

Intraobserver variability was evaluated using percentage agreement and calculating Cohen's kappa with confidence intervals for each pathologist. The kappa value for intraobserver agreement for repeat digital reads of the same case was 0.80, compared with a value of 0.78 for reads on the light microscope, and 0.80 for digital versus light microscopy reads. (See table 37). This equates to excellent intraobserver agreement with no evidence of inferiority of using digital, with the kappa value for digital versus digital reads non-inferior to the kappa for light microscopy versus light microscopy reads.

Modality	% agreement	Kappa value	Confidence interval
Glass slide v glass slide	85	0.78	0.57-0.81
Digital slide v digital slide	87	0.80	0.72-0.87
Glass slide v digital slide	87	0.80	0.70-0.90

Table 37. Intraobserver variability for breast lesion classification using digital and glass slides.

7.3.4 Discussion

Pathology services stand to benefit from the transferability and resilience of digital slide versus glass slide reporting, and there is great interest in using DP to report cases for the UK national cancer screening programmes including NHSBSP. For this specific use case, where healthy, non-symptomatic women are being screened, particular care must be taken to ensure that diagnostic quality and confidence are maintained or improved by the adoption of DP as a new platform of reporting. The data presented in this study relating to needle core biopsies includes both screen-detected and symptomatic lesions. In the screening setting the gold standard for histological diagnosis is the needle core biopsy. Some borderline lesions are over represented in the screen detected setting compared with the symptomatic setting, but the large number of cases in this study minimise this impact.

Systematic review data, and large non inferiority studies have demonstrated a high level of concordance between glass and digital slide diagnoses by pathologists.

The combined data for digital:glass concordance from the experimental concordance studies demonstrated a concordance rate of 98.7% for breast pathology cases,

validating the use of digital slides as replicas of the original glass slide. Data from direct comparison validation also indicated excellent rates of concordance, with an observed concordance of 99.1%. Further data from an intraobserver variation study of deliberately challenging NHSBSP specimens indicated an excellent level of agreement between glass and digital slide diagnoses for individual pathologists.

The majority of clinical discordances encountered in the experimental data presented were attributable to differences in mitotic count, with an observed tendency to underestimate the mitotic count on the digital slide. Two causes were identified for this by participants: first, a suggestion that less contrast between chromatin and the background on digital slides made mitoses harder to identify on initial low power assessment of the slide, and second, the inability to adjust the fine focus on high power examination of suspected mitotic figures on the digital microscope. A number of workarounds could mitigate difficulty in this area, including the use of adjunctive immunohistochemistry or the use of image analysis software to automate or semi-automate mitotic counts. It is interesting to note that Centre for Pathology, Vilnius, observed significantly more discordance than University Hospitals Coventry (4% versus 1%). One possible explanation for this might be the use of routine 20x equivalent scanning rather than 40x equivalent. A number of previous validation studies of digital pathology for various topographies have observed that pathologists found diagnostic accuracy and confidence improved using 40x scans, particularly for tasks dependent on small object detection [58, 69] (eg. micro-organism detection, granulocyte classification).

From our experience the most challenging diagnostic findings apart from the above

mentioned entities include stromal cellularity, which may make assessment of some phyllodes tumors difficult on digital images, assessment of the degree of cytonuclear pleomorphism and assessment of low grade atypia. In this study, the majority of the discordant cases observed were unlikely to impact of further management provided that MDT review was carried out, which is the routine scenario in the UK for management of screen-detected breast lesions.

The pathologists at all four clinical sites have found a number of benefits in reporting their work digitally, including:

- loss of glass slide transport and transfer delays
- rapid and convenient availability of images for sharing and second opinion
- rapid access to previous biopsies for comparison with resection/repeat biopsies
- Perceived increased efficiency in the diagnosis of large volume biopsies and multislide, multilevel cases
- Occupational health benefits. - one pathologist would have been unable to complete her breast screening workload on the light microscope one day due to a neck injury, but was able to complete her work on digital without a problem
- Enhanced opportunities to demonstrate pathology in MDT meetings
- Utility for teaching a larger cohort of trainees also facilitates inclusion of trainees from a distant site by connecting through video link, eliminating the need of travelling to site of teaching. The cases can also be visualised by

these trainees digitally in their own time hence avoiding any slide transfers between sites

- The feasibility of applying AI based tools in the routine setting of breast pathology reporting

The new digital pathology guidelines from the Royal College of Pathologists [1]describe the need for individual pathologists to be validated with sufficient rigour to satisfy an internal or external observer that safety and clinical effectiveness are maintained. This evidence supports the notion that digital pathology is non-inferior to standard light microscopy, for suitably trained and validated pathologists, and would support them to diagnose breast cancer screening programme specimens on digital slides.

Chapter 8 Conclusion

Digital pathology is a technology with the potential to revolutionise the way pathology services are delivered in the National Health Service, and worldwide, presenting opportunities to future proof an increasingly stretched diagnostic service whilst improving the quality and timeliness of cancer reporting. In undertaking this period of PhD study, the author sought to follow an evidence based approach to patient safety aspects of digital pathology use in the clinic, and in this way facilitate adoption in the NHS. This thesis presents a body of work in which a novel digital pathology training and validation protocol was designed, implemented and modified to adapt to diverse clinical use cases. Clinical adoption has been hampered by a lack of information and guidance regarding validation, training and patient safety. Much of the published literature regarding digital pathology in the clinic is targeted at "early adopter" clinicians, and assumes a certain level of technological knowledge, and an enthusiasm for WSI. For regional or national scale utilisation of digital pathology, a critical mass of practising pathologists working at diverse sites, and with diverse experience with and enthusiasm for digital reporting will have to be convinced they can work competently and confidently on the digital microscope. The author was motivated to produce and share documentation relating to training, education and patient safety topics, based on evidence based review of existing literature, and real world experience from trialling the training and validation protocol.

In chapter 1, background information was provided explaining the basic technology underpinning digital pathology, and describing the many potential benefits of, and

prevailing barriers to digitisation in the clinical pathology laboratory. Over the last three years, rapid progress has been made, and digital pathology is increasingly characterised as a mainstream clinical pathology topic rather than a niche application for the early adopter and the pathology informatician.

In chapter 2, the results of a nationwide survey of UK pathology departments was presented, revealing that at the start of this body of work, 41% of respondent departments were actively scanning glass slides, although these were predominantly for educational, research or quality assurance purposes. Low level use for primary or secondary diagnosis was reported by around a third of respondent institutions. Predictions of usage levels a year in the future suggested that an increasing number of departments expected to use digital pathology more frequently for clinical diagnosis. The majority of departments listed clinical digital pathology adoption as a high or essential level priority, and whilst the key barrier to implementation was cited as cost, departments would also value clear guidelines and statements from key professional bodies on how to adopt digital pathology without compromising patient safety or professional standards.

The findings from the survey prompted a detailed and innovative analysis of the digital pathology concordance literature to identify key training and safety points regarding WSI based primary diagnosis, which is presented in chapter 3. In the traditional validation literature, concordance and discordance rates are often reported without any discussion of the clinical implications in terms of patient outcomes or pathologist workload. Reassuringly, the types of errors or misdiagnoses made on digital slides were no more likely to cause significant patient harm than

those made on conventional glass slides. Thorough examination of discordant diagnoses recorded on the digital microscope allowed the identification of key "problem areas", where pathologists were more likely to encounter difficulty interpreting digital slides. These included the identification and grading of dysplasia, the location of small diagnostic objects and features, and the location and the identification and quantification of mitotic figures.

In chapter 4, this information was used to guide the development of learning targets for a validation and training protocol for digital pathology – the first of its kind, offering individualised training in primary diagnosis in real world settings. In chapter 5, this protocol was implemented in two diagnostic subspecialties at Leeds Teaching Hospitals, breast and neuropathology. Following a comprehensive validation procedure, excellent rates of clinical concordance were achieved by all participants, and from a clinical standpoint, it is important to note that since their validation period, all 5 pathologists (3 breast pathologists, 2 neuropathologists) complete all their primary diagnoses on the digital microscope as standard, only deferring to glass in a small number of specified clinicopathological scenarios (less than 1% of all cases), and in the case of breast pathologists, to satisfy PHE that key slides from screening cases have been reviewed on glass. Modification of the protocol, following the general approach utilising evidence based training sets of "difficult on digital" cases, and mitigating risk with glass slide checks or other safety nets in problematic scenarios, allowed for stand-alone training modules in two further use cases: frozen section assessment and immunohistochemistry assessment.

Finally, in chapter 7, guidance regarding safety aspects of clinical digital pathology was presented. A detailed, practical description of laboratory and diagnostic considerations for obtaining ISO 15189 accreditation for clinical digital services was provided, and applied to achieve the UKAS accreditation for digital diagnosis at a large fully digital NHS laboratory. Data regarding the safety of digital slide for breast cancer screening patients was collected and analysed, using experimental and "real world" validation data from 4 European cancer centres. An accumulation of evidence from diverse sources suggested cautious optimism for the use of digital slides in breast cancer screening programme specimens. The majority of clinical discordances encountered in all experimental studies were attributable to differences in mitotic count, which would not have affected clinical outcome for the patients in question.

One of the key enabling factors for digital pathology implementation raised by participants in the survey discussed in chapter 2 was access to more information and guidance on safe implementation. The contents of this thesis have been disseminated widely amongst both the pathology informatics/ digital pathology community and the general clinical pathologist publication. A suite of peer reviewed scientific papers resulting from this work[27, 47, 85, 87, 89-92] have been complemented with major presentations and invited speaker plots at leading international digital pathology conferences (eg. Pathology Visions (2017,2019) and Pathology Informatics (2017, 2020) in addition to national general pathology conferences in 10 countries. The content of the thesis is also presented in a more personal way at the Leeds Digital Pathology workshops which were designed by the author, and delivered with the support of other Leeds digital pathology team members. (See figure 23).

Figure 23. The author delivering a session on digital pathology implementation at one of the Leeds Digital Pathology Workshops in 2018.

To date 8 workshops and have been held, and more than 150 delegates have been invited to the department to see digital pathology in action, and learn about the evidence base, training and validation. Some of the content from the workshops is replicated in the Leeds Guide to Digital Pathology, an accessible overview summary of key topics in digital pathology implementation aimed at pathologists, laboratory managers, IT professionals and policy makers.

In addition, the author has delivered bespoke validation workshops in Switzerland and Denmark to aid regional digital deployments, and contributed to digital pathology guidance documentation on behalf of the Royal College of Pathologists and the European Society of Toxicologic Pathology.

The work described in the thesis has several limitations, including the relatively small number of pathologists included in the validation protocol trials (chapters 5 and 6), and the setting of these studies being limited to a single teaching hospital, Leeds Teaching Hospitals NHS Trust. The studies detailed in chapter 7 include data from 4

different institutions in 2 countries, the UK and Lithuania, but 3 of these are major cancer centre/ teaching hospitals. Since its publication, the primary diagnostic validation protocol has been utilised in a number of other institutions across the world, including hospitals in Oxford, Lincoln and London in the UK, and Linköping in Sweden. It will be interesting to compare attitudes to the validation process itself, as well as collect more data on areas of diagnostic difficulty. The protocol is easily modified for the general pathologist, as described in chapter 7, and will shortly be rolled out to a further 6 district general hospitals in West Yorkshire as part of the Northern Pathology Imaging Co-Operative clinical network, a £17 million project funded by the Industrial Strategy Challenge Fund and industry partners.

As experience with digital pathology broadens, it will be possible to gather more data on challenging areas of digital diagnosis. Sharing of this data will not only allow pathologists to improve existing training and education resources for digital reporting, it could also be used to influence the design of new digital pathology hardware and software which could improve diagnostic accuracy and confidence. Beyond this, the data might be used to prioritise appropriate features and tasks for the development of AI applications which can support the pathologist with difficult areas.

The necessity for further research and development work in several specific areas has been identified following on from this body of work. Foremost amongst this is the need to address the challenge and opportunities presented by artificial intelligence (AI). The success of deep learning techniques render the possibility of hybrid human/computer assisted diagnosis of pathology images in the near future

more likely than ever. With this in mind, the pathology community will have to think carefully about how AI applications should be validated for clinical use, especially in the case of "human in the loop" products, which depend upon a combination of computer and human intelligence working in tandem to produce a diagnosis or assessment. One way of validating the performance of an AI application is the use of feature studies, where the ability of the algorithm to detect certain diagnostic features in a field of view is compared with the ability of a pathologist to perform the same task. For this type of study, it is important that the features chosen are clinically relevant. The evidence based list of diagnostic features detailed in chapter 7 of this thesis (Table 29).

In the last few weeks before submission of this thesis (March 2020), the Coronavirus pandemic emerged as a major challenge to health services across the world. Sick leave, self-isolation and carer duties have resulted in unprecedented staffing issues, whilst departments battle to clear diagnostic backlogs. Digital pathology, as an enabler of remote working in diagnostic pathology, could help support those needing to self isolate, and allow them to continue vital diagnosis from home. Whilst some individuals have experience of this, little work has been done to determine optimum conditions for home reporting, including technical and training considerations.

This publication produced in response to the pandemic provides information regarding risk assessment of home reporting of digital slides, summarises available information on specifications for home reporting computing equipment and shares access to a novel point of use quality assurance tool for assessing the suitability of home reporting screens for digital slide diagnosis.[94] What is needed is evidence based

evaluation of home reporting systems, and particularly display screens, to ensure that the high standards of diagnosis that are aimed for in the hospital are replicated in the home office.

In 2017, when the work contained in this thesis commenced, a lack of guidance and reassurance, particularly regarding patient safety, training and validation was a significant barrier to widespread clinical adoption of digital pathology. It is the authors hope that in conducting a comprehensive and novel analysis of the evidence base, creating innovative validation protocols, training materials and guidance documents and disseminating work through scientific publications, presentations and workshops, pathologists now have access to pragmatic material which can advise and assist them in transitioning from conventional light microscopy to digital microscopy.

List of abbreviations

Abbreviation	Expansion
AI	Artificial intelligence
CAP	College of American Pathologists
CE	European Conformity
CLIA	Clinical Laboratory Improvement Amendments
CM-Path	Cellular Molecular Pathology
CMV	Cytomegalovirus
DCIS	Ductal carcinoma in situ
DP	Digital Pathology
ER	Oestrogen receptor
FDA	Food and Drug Administration
H&E	Haematoxylin and eosin
Her2	Human epidermal growth factor receptor 2
IHC	Immunohistochemistry
ISO	International Organisation for Standardization
JPEG	Joint photographic experts group
LIMS	Laboratory Information System
LVM	Leeds Virtual Microscope
MDT	Multi-disciplinary team
MDTM	Multi-disciplinary team meeting
NCRI	National Cancer Research Institute
NHS	National Health Service
PHE	Public Health England
PR	Progesterone receptor
RCPath	Royal College of Pathologists
SOP	Standard Operating Procedure
SV40	Simian virus 40
SWEDAC	Swedish Accreditation Body
TAT	Turn around time
UKAS	United Kingdom Accreditation Service
WHO	World Health Organization
WSI	Whole slide image

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