



The Royal College of Pathologists

Pathology: the science behind the cure

Best practice recommendations for implementing digital pathology January 2018

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Foreword

Whole slide imaging is a technology that has the potential to transform the practice of pathology. Uptake and experience of digital pathology has been relatively low, but now several laboratories in the UK have already implemented or are about to implement digital pathology using whole slide imaging, having evaluated the balance of risks and benefits for the work of their laboratories.

These Best Practice Recommendations (BPRs) provide an overview of the technology involved in digital pathology and of the currently available evidence on its diagnostic use, together with practical advice for pathologists on implementing digital pathology.

The authors based these BPRs on published evidence, including the only registered published systematic review of the literature, and personal experience of using and developing digital pathology systems.

The practical advice is based on pragmatic, pathologist-led self validation incorporating evidence-based training and experiential learning on real world cases. It avoids the need for each implementation to perform a diagnostic accuracy study or clinical trial.

These BPRs were developed without external funding to the writing group. The College requires the authors of such documents to provide a list of potential conflicts of interest; these are monitored by the Director of Clinical Effectiveness and are available on request.

This is a rapidly evolving area and we expect these BPRs will be updated on a regular basis as evidence and experience accumulates.

The stakeholders that are being involved in the consultation are:

- Institute of Biomedical Science (IBMS)
- British In Vitro Diagnostics Association (BIVDA)
- United Kingdom National External Quality Assessment Services (UKNEQAS).

1 Introduction

1.1 Context and definitions

Telepathology is the electronic transmission of pathological images from one location to another, for the purpose of interpretation and diagnosis. This has in the past been by means of a remote-controlled microscope. Telepathology has been used internationally for many years, mostly in small-scale deployments for limited clinical use (e.g. frozen sections). The Royal College of Pathologists issued guidance for telepathology in 2005, updated in 2013.

Whole slide imaging (WSI) is a relatively new technology that allows the digitisation of an entire glass slide, producing a digital image for review.

The adoption of whole slide imaging is at an early stage, with a limited number of clinical deployments in the UK and worldwide, and relatively little formal clinical or technical research to inform its use. The published research on the validation of digital pathology is limited to clinician-driven studies in single hospital deployments. No large national clinical trials of digital pathology have been performed.

Pathologists often don't have as detailed knowledge of the advantages and limitations of this technology compared to their expertise in pathology or histotechnology.

1.2 Purpose

These are professional recommendations for pathologists wishing to use digital pathology while maintaining patient safety. They incorporate and update relevant parts of the telepathology guidance (2013).

In issuing BPRs and other guidance it is important to acknowledge that the current evidence in this area is not plentiful or uniformly of high quality but what evidence is available will be summarised.

These BPRs include a brief section on the technical aspects of digital pathology, as a background for pathologists who are unfamiliar with the technology.

This document aims to give pragmatic and specific guidance on validation and verification of digital pathology for clinical use – with an appendix giving useful procedures for validation. This is not intended to be prescriptive.

Examples of areas of diagnostic pathology where studies indicate a risk of discordant diagnostic options are cited so that pathologists are aware of potentially problematic areas. Advice on mitigating these problems is provided.

1.3 Scope

These BPRs include the use of both conventional telepathology systems and newer whole slide imaging (digital pathology) systems.

The clinical domains of histopathology including frozen sections are included in the scope.

Cytopathology is considered to be out of the scope of this document, due to the lack of evidence in this specialised area. However, pathologists considering the use of telepathology or digital pathology for cytological diagnosis could use the recommendations in this document as a basis for establishing safe practice.

1.4 Updates

Digital pathology is a rapidly developing area, both in terms of development and deployment. This group expects to update and/or expand these BPRs regularly to incorporate additional knowledge/evidence as it arises.

2 Background

2.1 Need for digital pathology

Digital pathology offers a number of potential benefits as it enables electronic transfer of slides from the laboratory to the pathologist. This enables improved workflow in the laboratory, allows work to be shared across sites, and allows extension and reorganisation of subspecialist reporting. These factors are potential solutions for local shortages of pathologists.

Digital pathology also makes it easier to share cases between multiple pathologists. The ease with which second opinions can be sought may help to improve the overall quality of services. A more systematic summary of the benefits of digital pathology has been published recently.¹

For these reasons many pathologists and institutions are using or contemplating whole slide imaging for diagnosis.

2.2 Safe adoption of digital pathology

As with the adoption of all new technologies, there is a need to balance the benefits of adoption against the associated risks. Comprehensive evidence of the safety of digital pathology in all settings is unfortunately not yet available. Pathologists should seek to ensure safe clinical practice at all times.

The US FDA (Food and Drugs Administration) guidance to manufacturers recommends that medical devices should have established safety (i.e. a reasonable assurance that the benefits of the device outweigh the risks) and effectiveness (i.e. a reasonable assurance that the device will provide clinically significant results).² These principles are applicable to the clinical use of the devices by pathologists too.

When introducing telepathology or whole slide imaging, pathologists should ensure the quality of their diagnosis with digital pathology is equivalent to the current standard (using conventional light microscopy).

It is worth noting that adoption of digital pathology can increase the safety of a diagnostic service in other ways (e.g. by reducing the risk of patient misidentification, or increasing access to second opinions).

2.3 Distinction between telepathology and whole slide imaging (WSI)

Conventional telepathology comprises a remote-controlled microscope to provide a live view of a tissue sample. Telepathology has been used in this way for many years to make diagnoses, usually for small numbers of cases. Digital pathology is a general term for the use of digital imaging in pathology, but the key technology enabling digital pathology is 'Whole Slide Imaging', a technology which creates a digital image of the entire glass slide for later review.

Pathologists should be aware that, while telepathology and whole slide imaging share many similar characteristics (e.g. the use of microscope optics, image capture devices, and viewing software) there are some important differences:

- telepathology is usually employed for low-throughput activities, where a remote diagnosis is requested, often in the context of a second review or preliminary diagnosis in a situation where an on-site pathologist cannot be obtained (e.g. on frozen section). Digital pathology with whole slide imaging has the potential to be used for larger workloads, including bulk reporting of cases for primary diagnosis, replacing the light microscope.
- many telepathology systems allow the remote control of the microscope directly, including the fine focus mechanism. This allows the pathologist to select the area and adjust the focus to their satisfaction. Whole slide imaging systems often capture a 2D image of the whole slide, removing the ability of the pathologist to control the fine focus in a specific area on demand. In most areas of diagnostic practice this appears not to be a significant factor but pathologists should be aware that this has the potential to reduce their ability to see some diagnostic features compared to conventional telepathology.

2.4 Concordance studies for whole slide imaging

Several validation studies for whole slide imaging (WSI, digital pathology) have been published, and most show broad concordance between the digital diagnosis and the conventional microscope. However, the vast majority of these studies lack adequate size and statistical power.

A systematic review of WSI has shown some evidence for the accuracy of whole slide imaging, but the overall quality of the evidence is not high, and many studies are small. Goacher *et al.* reviewed 1,155 abstracts, of which 38 papers were included in the systematic analysis.³ The overall diagnostic concordance between WSI and conventional microscopy ranged from 63% to 100%, with a weighted mean of 92.4%. Kappa values ranged from 0.29 to 1.00, with a weighted mean of 0.75. For comparison, the mean diagnostic concordance of light microscopy in those studies that reported it was 93.4%.

Problems with the existing literature in the systematic review include:

- the quality of evidence is very variable with heterogeneous study designs, and there are few high-quality studies
- small sample sizes have been used in most studies – only two studies included in the above systematic review had more than 400 cases, and many employed relatively small numbers of readers
- incomplete information was provided about procedures (e.g. image compression or type, or the model of display was not specified)
- appropriate sample size calculations and statistical tests (e.g. non-inferiority testing) were not always performed
- there is a risk of publication bias (e.g. unsuccessful implementations with high discordance were abandoned or not published, or published studies are from a self-selecting group of early adopters)
- no large, multicentre controlled trials have been published
- transferability of the evidence between devices or situations cannot be assumed. For example, evidence of validation of an instrument from one manufacturer does not mean that other manufacturers' instruments will behave similarly.

A more recent study in the UK, the largest published study to date, included 3,017 cases⁴ with a non-inferiority design and prior sample size calculation. It demonstrated no inferiority of digital diagnosis compared to the light microscope and complete concordance or no clinical difference in 99.3% of cases (95% confidence interval 99.0 to 99.6).

A large manufacturer-sponsored diagnostic accuracy study was published in 2017 and used to support FDA approval for a digital pathology system. It reported non-inferiority of digital pathology in 2,000 surgical pathology cases read by four pathologists per case in four centres, with a 0.4% difference in major discordance rate between whole slide imaging and light microscopy (95% confidence interval -0.30 to 1.01%).⁵

2.5 Discordances in digital pathology

A systematic review of the discordances reported in the published validation studies⁶ includes 23 papers in which a description of discordances was given and provides insight into those areas where pathologists might need to exercise caution:

- these 23 papers included 8,069 pairs of digital-glass reads
- in total, 335 (4.2%) discordant interpretations were noted
- of these 335 discordances, the light microscope diagnosis was preferred in 286 cases (85%) and digital diagnosis was preferred in 44 cases (13%), with an equivocal response in the remaining six cases (2%)
- in terms of potential for patient harm, of the 335 discordances:
 - 60 discordances had no potential for harm
 - 242 had potential for minimal or minor harm

- 28 had potential for moderate or severe patient harm.
- of the 28 discordances with the potential to cause moderate or severe patient harm, glass was the preferred diagnostic medium for 26 (93%), with digital microscopy preferred in two (7%).

Limited evidence in the literature suggests that diagnosis on virtual slides may be more difficult in certain types of pathology⁶ including:

- dysplasia of epithelial cells (e.g. squamous, urothelial, or glandular), possibly in those areas where the assessment of nuclear texture is important
- detection of small objects (e.g. micro-organisms, foci of acute inflammation in epithelia)
- assessment of large areas of tissue for rare events (e.g. micrometastases).

Pathologists using digital pathology to make diagnoses should be aware of these potential limitations. They should also be aware that there may be specialty-specific issues that they should be familiar with. For example, weddelite (calcium oxalate) crystals in breast samples are often detected using polarised light, which is not available with current digital pathology systems.

2.6 Regulatory approval

Whole slide imaging devices are medical devices, and as such, instrument manufacturers are required to obtain regulatory approval before selling a device for diagnostic use. A medical device must undergo quality control of design and manufacturing, and have a service and quality assurance programme.

In Europe, some whole slide imaging instruments have regulatory approval for diagnostic use (indicated by the CE Mark for in vitro diagnostic devices, or CE-IVD).

In the US, the FDA regulates the sale of medical devices. Pathologists should be aware that the level of evidence required for CE-IVD marking may be lower than that required for FDA approval. FDA approval for primary diagnosis has recently been granted for one of the commercially available WSI systems in April 2017.⁷

These regulatory bodies serve to regulate the device manufacturers, not the medical professional's use of the device.

Pathologists should ensure the instruments they use have regulatory approval for the intended use. Deviation from regulatory guidelines is equivalent to 'off-label' use of a medicine – pathologists and institutions should do their own risk assessment of 'off-label' use. A validation and verification procedure will be relevant regardless of regulatory approval.

Instrument manufacturers will have performed some concordance studies during the device approval process. These studies may not be published in the scientific literature. Pathologists may find it useful to request this information from the manufacturer during a deployment or procurement process so they can understand what level of validation has been performed during the approval process.

2.7 Current professional and laboratory guidelines

2.7.1 Royal College of Pathologists Telepathology Guidelines 2013⁸

These BPRs cover many relevant general issues (e.g. security, standards) but do not provide specific guidance to pathologists on the validation and verification of digital pathology for clinical use. Given the increasing need for larger-scale adoption of digital pathology, more specific guidance was felt to be necessary.

2.7.2 Royal College of Pathologists Guidelines for Cellular Pathologists on Reporting at Home 2014⁹

These guidelines covers the areas of governance, confidentiality, record keeping, result transmission and audit and is relevant when digital pathology is used to report remotely from home.

2.7.3 College of American Pathologists Guidelines 2009

The US College of American Pathologists (CAP) guidelines were an early attempt to provide information for professionals about validation and implementation of digital pathology.¹⁰

Important points made in the CAP guidelines and endorsed by the College are:

- the need for every laboratory using WSI to carry out a validation/verification, appropriate to their own clinical use and setting, in a real world environment
- the need to consider the whole system (from scanner, to pathologist workstation) in the validation/verification process
- the need to validate/verify the system for each intended use of the system (e.g. frozen sections, gastrointestinal pathology)
- the need to re-validate if significant changes are made to any component of the system (e.g. a new scanner is introduced, or different displays are used)
- the importance of training in the use of the system.

The current College guidelines differ from the CAP guidelines in a few ways:

- the aim of the CAP guidelines was to 'validate' the use of digital pathology but they do not offer guidance if complete validation is not possible (e.g. if certain cases are not safely diagnosable on digital). Since the CAP guidelines were published many digital pathology deployments are finding that, in practice, 100% digital reporting without deferral to glass in some cases is not practical or possible.
- a laboratory validation does not obviate the need for larger scale evidence of safety (e.g. clinical trials or the evidence submitted for regulatory approval). Pathologists should also be aware that vigilance is required after the validation period, and as with the light microscope pathologists' performance with the system should form part of routine laboratory internal and external quality assurance.
- the CAP validation procedure mixes aspects of laboratory quality assurance procedures (e.g. comparing the standard light microscopy with digital pathology for a validation set of cases) and those more often seen in a randomised trial (e.g. a washout period of two weeks or more between glass and digital), which may be difficult or unnecessary for pathologists to implement in clinical practice
- a sample size of at least 60 cases was recommended based on the limited evidence from the literature as "it tends to result in better accuracy and concordance than an average of 20 cases and almost similar accuracy and concordance to an average of 200 cases". Many pathologists now cite that figure of 60 cases as the minimum sample size required to validate digital pathology. The sample size is similar to that used (for example) in validation of new immunohistochemical stains in the laboratory. This may be an appropriate number when the user is highly familiar with the technology. But given the relative novelty of whole slide imaging, which is an entirely new way of working, and most pathologists' inexperience with the technology, it may not be sufficient for the proper verification of the diagnostic utility of the technology or learning of the pathologist. 60 cases could be less than one day's workload for some pathologists, which may not be sufficient to convince a reasonable external observer that the pathologist has sufficient experience and knowledge of the technique to be as competent as the microscope.

- an external observer may be more likely to see reasonable evidence of safety and effectiveness if a validation/verification included consideration of case numbers, case mix, duration of validation and individual competence. A flexible approach with time and/or numerical guidelines, modifiable depending on the application, and extendable where necessary, may be more appropriate for the introduction of this technology.

2.7.4 Accreditation standards

Accreditation using ISO 15189:2012 includes comparison of new technologies against the existing standard. Evidence from the training period and ongoing monitoring should assist in complying with the standard.

2.7.5 Validation and verification terminology

ISO 9000:2000 defines verification as “confirmation, through the provision of objective evidence that specified requirements have been fulfilled.” Verification is often used to confirm that a laboratory test is being used correctly as intended by the manufacturer – for example in a well-established laboratory test with full regulatory clearance.

Validation is defined as “confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled”. In laboratory practice this is used to confirm that a test meets the need of the user, for example to validate that an in-house test or significant change to a test is appropriate.

Given the current status of digital pathology, sufficient evidence of established use or appropriate standards are immature, pathologists may need to undertake elements of both verification and validation. In this document, the compound term validation/verification is used throughout.

3 General background information on digital pathology

A short summary of the relevant background to digital pathology is provided here for information. Imaging science is complex and spans the domains of optics, hardware, software and psychology. This summary is not exhaustive, and there are many areas in which more research is needed to develop further the science and practice of digital pathology. Pathologists may wish to do further reading to better understand some of the issues below.

3.1 Imaging science

Pathologists should be aware that a digital image is a high resolution replica of a section on a glass slide, but it is not an exact replica in every way.

A microscope is an optical device that allows a pathologist to directly observe the stained tissue. A digital image is an attempt to capture and replicate that physical object. The imaging device is the product of an engineering process in which design decisions are made which affect what information is captured and presented to the pathologist. Different design decisions will affect the appearance of the final image.

Pathologists are experts in the assessment of tissue preparation and staining, and of artefacts introduced in tissues as they are prepared. They may not yet have the knowledge or skills to assess digital imaging artefacts or quality in the same way.

An image may appear to be high fidelity (i.e. like the microscope) and visually pleasing (with high brightness and contrast and saturated colours), but may lack information (e.g. contrast in medically relevant parts of the image) that can directly or subconsciously impact on image interpretation.

While device manufacturers make efforts to generate microscope-like images, pathologists should be aware that an image may be visually pleasing but image quality or “fitness for purpose” (e.g. diagnosis of dysplasia) does not always correlate with the subjective assessment of visual appeal.

Digital pathology consists of an end-to-end imaging chain. Pathologists should be aware that the same tissue sample may look different when imaged/scanned with different instruments, viewed on different displays, or even assessed with different software viewers.

3.2 Scanner technology

3.2.1 Scan magnification

Whole slide imaging devices use microscope objective lenses to acquire images. These are usually 20x or 40x lenses. Some employ a 20x lens with a “doubler” lens to produce a 40x magnification.

Pathologists should be aware that the final perceived magnification (i.e. the relative size of the object on the display) can be affected by many factors including the acquisition magnification, the zoom level chosen in the viewing software, the size and spacing of the camera pixels, the size and spacing of the pixels on the display and how far the eye is from the display. Unless the WSI system has been specifically designed and configured to do so, an object in an image displayed at 20x on a display is unlikely to be exactly the same size as on the microscope at a similar nominal magnification.

Some viewers allow ‘digital zoom’, which increases the apparent magnification on screen. This can be useful in some circumstances, but pathologists should be aware that no additional information is being added to the image during a digital zoom.

When training with a whole slide imaging system pathologists should compare the image on their microscope at varying magnifications to familiarise themselves with the similarities and differences between the two.

3.2.2 Scan resolution

Manufacturers often specify the resolution of their device – for example 0.5 microns per pixel for a 20x scan, and 0.25 microns per pixel for a 40x scan. Resolution is the ability of an optical system to separately identify two nearby points in the imaged object. The resolution of the acquired whole slide image is affected by several stages in the optical imaging chain, including the magnification of the objective lens used, the camera chip design and the electronic components inside the device. Pathologists should assess for themselves the overall resolving power of their whole slide imaging device, for example by comparing the appearances of small details (e.g. nuclear chromatin) on the microscope and the WSI system.

3.2.3 Scan plan and out-of-focus areas

As tissue sections have a 3D structure on the slide, but scanners produce a 2D image, many whole slide imaging devices use a 3D ‘scan map’ or ‘scan plan’ to plan slide scanning. These typically work by detecting all the tissue pieces on the glass slide, adding focus points to the image before or during scanning, then moving the focal plane of the objective lens to optimise focus at each point. In so doing, the scanner generates an optimised 2D representation of the tissue at each focus point, but will interpolate the lens position between focus points.

For example, if a scanner focusses on some dust or marker on the slide coverslip, then the focal plane of the scan around that will be higher than the tissue, leading to out-of-focus areas of tissue in the image.

Pathologists should be aware of the means by which their WSI system scans tissue, so they can understand artefacts introduced by focussing or scan planning.

3.2.4 Depth of field and 'z-stacking'

Microscope objective lenses have a 'depth of field' in which the image is in focus. For example a typical 40x lens on a diagnostic microscope has a depth of field of about 0.5 microns – significantly thinner than the thickness of a typical section (approximately 3–5 microns). Pathologists will be familiar with this, and use the fine focus mechanism of their microscope to move the focal plane of the objective lens up and down through the tissue, so they can visualise the entire piece of tissue from top coverslip to bottom glass slide.

In contrast, whole slide imaging devices typically capture a single image plane across the entire slide. The resulting image will have a depth of field fixed by the WSI device optics.

Some scanners offer the capability to capture a 'z-stack' of images across the entire slide. This allows the pathologist to see (for example) a stack of 10 images, each spaced at 0.5 microns, with a total effective depth of field of 5 microns. Pathologists often appreciate the greater view of the tissue that this affords them. However, z-stacking increases both the scan time and the amount of data generated by WSI systems.

The opinion of experienced users suggests that z-stacking is not necessary for the majority of surgical specimens but it is not known whether it helps in the assessment of difficult cases.

3.2.5 Stitch error/stripping

It is not possible to capture an entire whole slide image at once. Most WSI devices capture contiguous images from the glass slide either as tiles or stripes, by moving the objective lens/imaging system relative to the glass slide. These sub-images are then stitched together to create the whole slide image.

Pathologists should be aware that this stitching can produce artefacts such as visible striping or misalignments across tiles. In some cases misalignment could result in small areas of tissue being hidden – manufacturers would consider this to be an operating error. During assessment and use of WSI devices pathologists should ensure stitch artefacts are minimised.

3.2.6 Tissue coverage

WSI devices reduce the time taken to scan the entire glass slide by minimising the scanning of 'empty' parts of the slide. Manufacturers differ in the methods they use. Some WSI systems automatically detect the tissue pieces, and scan the tissue with minimal empty glass slide around them. Others generate a bounding box, which encompasses all the tissue pieces, and scan the entire area including empty glass. If the tissue detection system of the WSI device fails to find all the tissue on the slide, then the resulting image will be inadequate. This has been known to happen with pale or scanty tissue sections (e.g. fatty tissue in the breast).

Pathologists should be aware of the risk of incomplete tissue coverage in a scan, and have procedures in place to ensure all tissue is scanned.

3.2.7 Displays

Pathologists should be aware that display resolution, brightness and contrast can affect the appearance of the image. The display is a very important part of the digital imaging chain.

The consistency of the display over time and between instruments are important features to consider.

In the fields of radiology and professional colour work (e.g. photography, printing), control of luminance and colour are seen as central issues, and high grade displays are used. Extensive research and guidelines exist in the radiology domain governing the use and assessment of displays.^{11,12}

Displays exist (so-called 'medical grade' displays) which guarantee control over brightness and contrast and have been proven to be fit for the intended use in a medical setting for

primary diagnosis. Alternative, so-called ‘review displays’ exist which are lower cost but are considered suitable for lower risk uses (e.g. the review of radiological images on the ward). As such, a clear link has been established between the intended use of the display and its specifications. However, these displays have been developed, assessed and approved mostly for radiological imaging, where luminance is known to be important (e.g. it affects the perception of lesions on mammograms) and images are pseudo-colour. Further work is required to fully establish the requirements of a display for digital pathology.

Manufacturers often have displays with high brightness, contrast, colour reproduction, etc suited for imaging which they market for professional imaging uses, but which are not marketed as ‘medical grade’. Additionally, modern consumer grade displays often have high specifications in terms of resolution, brightness and contrast, etc that may be sufficient for digital pathology use, but evidence for this is lacking.

Owing to financial constraints, some digital pathology implementations may use displays other than those marketed as medical grade. If doing so, then consideration should be given to the display quality issues mentioned above, and maintenance of these displays. Pathologists may wish to perform a risk assessment in choosing their displays – advice from institutional IT or Medical Physics departments may be helpful.¹³

Pathologists should be aware that ambient lighting and reflections can affect the performance of a display. In radiology, ambient light levels are kept low to allow detection of subtle contrast differences in grayscale images, and direct reflections on the display are minimised.¹⁴ Evidence is lacking in this area for pathology but experience from the colour print industry would suggest that controlled lighting conditions in a room with light levels suitable for reading printed material would make sense for colour digital pathology images, until further evidence is available.

Examples of displays used in current digital pathology deployments and the largest validation studies are listed below.

Location	Manufacturer and model	Resolution (width x height, megapixels)	Other specifications/ configuration
Coventry ⁴	Hewlett Packard ZR2440wL	1920 x 1200, 3 MP	Non-medical grade Calibrated using SpyderPro calibration system from Datacolor Inc.
Leeds ⁷	Barco MDCC6430	3280 x 2048 6 MP	Medical grade Gamma set to 2.2 sRGB calibrated luminance 400 cd/m ² (calibrated)
Philips FDA approval study ⁵	PP27QHD	2560 x 1440, 4 MP	Medical grade Gamma set to 2.2 sRGB calibrated luminance 350 cd/m ²
Linköping, Sweden	Eizo RX850	4096 x 2160, 8 MP	Medical grade Gamma set to 2.2 sRGB calibrated 400 cd/m ² (calibrated)

3.2.8 Image compression

Whole slide digital images are very often compressed to reduce the overall amount of data produced. Compression is a necessary part of digital image storage and transmission.

Compression may be 'lossless' or 'lossy'. Lossless compression (e.g. LZW compression) uses algorithms which allow the exact reconstruction of the image data from the compressed file. This has the disadvantage of creating slightly larger image files.

'Lossy' algorithms (e.g. JPEG or JPEG2000) compress the files to a much greater extent, by permanently discarding some of the image data. They take advantage of the relative insensitivity of human vision to certain kinds of information loss (e.g. JPEG compression prioritises the preservation of brightness information over colour information, as human vision is relatively insensitive to colour variation). The degree of compression applied can be increased as more information is discarded from the image. However, higher compression rates can introduce artefact.

The ideal compression algorithm would be completely 'lossless' in that no information is lost from the image. In practice, compression algorithms which are "visually lossless" are often accepted as being sufficient – i.e. they allow loss of image data (and smaller file size) without being apparent visually to the observer.

Further work is required to understand the full effects of compression on pathology images and diagnosis. These effects may be task dependent.

Pathologists should be aware that the compression algorithm used, and the amount of compression applied, may affect the final image in a digital pathology system.

3.2.9 Colour

Pathologists implementing digital pathology have noted that there are differences in colour reproduction between WSI systems and the microscope, as well as between WSI systems.

Imaging devices employ a procedure called "colour calibration" to ensure consistency and reproducibility of colour in the imaging chain.

Imaging standards for the reproduction of colour are still in development in digital pathology and the impact or otherwise of colour correction is not known. However it is sensible to ensure that alterations to colour are controlled and minimised in digital pathology. FDA guidance supports this.¹⁵ 'Test objects' or phantom slides may be a useful way of characterising the imaging chain and colour changes.

Pathologists should be aware of the differences in colour reproduction between devices, especially for their chosen device. In procuring devices, pathologists may wish to include an assessment of colour accuracy in their testing. Experience suggests that H&E, PAS and H-DAB immunohistochemical stains are most often affected by colour differences in WSI.

3.2.10 Quality assurance and calibration

Medical devices should undergo appropriate quality control and calibration before leaving the factory, and ongoing quality assurance thereafter. Research in this area is sparse, but the following areas are thought to be relevant:

- measurement of size – WSI devices usually come pre-calibrated, so that measurements on the digital image can be made to a high degree of accuracy. Pathologists should take steps to ensure these measurements are accurate and consistent as part of ongoing quality assurance and to comply with ISO 15189:2012.
- white point – WSI devices usually provide some procedure for the correction of illumination differences in the image, by means of a quality check (e.g. daily or before each scan)
- colour – control and quality assurance of colour may be included in the device quality assurance procedures.

Calibration slides may be helpful as part of internal and external quality assurance.

Technical external quality assurance schemes for digital pathology (e.g. to assess the image quality produced by the laboratory) will be necessary as this technology becomes more widespread. Interpretative external quality assurance schemes may decide to use whole slide images in their circulations – further guidance in this area will come from the College guidance on interpretative EQA.¹⁶

3.2.11 Image analysis

These BPRs relate to the human interpretation of digital pathology images. The authors are aware of image analysis algorithms that can assist with or automate the interpretation of H&E or immunohistochemically stained images.

The use of image analysis is often promoted as being beneficial and having the potential to reduce effort and increase reproducibility in certain diagnostic areas, such as the interpretation of immunohistochemical stains, or the detection of rare events (e.g. micrometastases, mitoses).

Pathologists should ensure that such systems are properly evaluated before introduction to clinical use, and that their strengths and weaknesses are understood.

Image analysis systems should also undergo specific validation/verification processes before their introduction into clinical workflows.

It is very important to recognise that the interpretation of microscopic images is not simple, and is a holistic process involving the interpretation of subtle image features using clinical knowledge and experience. It will likely be very difficult to automate this human task entirely.

Automation of simple tasks may be possible (for example pattern recognition of micrometastases), but this is a very immature area and further research is needed.

Pathologists should be aware of the history of computer-aided diagnosis in radiology which, despite significant hopes, has failed to have a significant impact on the workload or accuracy of radiological diagnosis to date, for a variety of reasons.¹⁷

As the use of image analysis evolves, the College will issue further recommendations on its use and validation/verification.

3.2.12 Efficiency

Claims of increased efficiency of pathology services with digital pathology are often made. The use of digital pathology has obvious benefits in the rapid referral of cases between institutions or across pathology networks.

Evidence of increased efficiency of digital pathology in the primary diagnosis compared to the microscope is lacking. Limited evidence in early deployments suggested that reading digital pathology slides was slower than the microscope.^{18,19} Little evidence has been published about the efficiency of modern digital pathology systems but those who have adopted digital pathology report satisfaction with overall speed compared to the microscope. Pathologists should make their own assessment of the potential efficiency benefits of digital pathology in their own environment, including the end-to-end workflow as well as the efficiency of the digital reading of pathology images.

4 Laboratory technical considerations for digital pathology

4.1 Specimen identification

Laboratories should have processes in place to ensure continuity of specimen identification from the glass slide to the digital image. This might include manual processes or automated processes such as barcoding.

4.2 Sectioning and staining quality

Pathologists should be aware that high quality mounted sections on glass slides produce higher quality digital images. Departments that use digital pathology often report a need to maintain high histotechnology standards to facilitate high quality scanning. Some departments have reported better imaging results from using thinner sections. Artefacts such as faint staining, scoring, debris, pen marks and coverslip problems can also interfere with scan quality.

4.3 Scan quality assessment

4.3.1 Focus

Laboratories should ensure that processes are in place to assess focus quality of digital images and rescan where appropriate.

Entirely out of focus slides, or those with large areas out of focus, should be rescanned. Interaction between pathologist and laboratory technicians may be necessary in determining appropriate levels of focus quality for a service.

Some digital pathology scanner instruments include a metric of focus quality, which may be of assistance in quality control of focus.

If pathologists review a slide with out of focus areas, they should use their judgement to decide if the artefact will interfere with their safe diagnosis of the image, and order re-scans as necessary.

4.3.2 Tissue coverage

Many whole slide imaging devices include systems to detect the location of tissue pieces on a slide, and limit scanning to relevant tissue-containing areas.

Sometimes, whole slide imaging systems produce an incomplete slide scan which misses part of the slide containing tissue.

Departments should ensure that laboratory processes are in place to ensure all tissue on the glass slide is scanned and included on the digital image. Such processes would be similar to current practice of comparing the tissue block to the glass slide.

Whole slide imaging systems may provide the functionality to assist the detection of, or avoidance of, missing tissue. These include (a) providing an overview image of the entire glass slide (rather than a cropped image of the scan area only) and (b) comprehensive whole slide imaging of all the glass rather than selected region-only imaging of pre-detected tissue areas.

4.4 Data retention policies

College recommendations are currently to retain glass slides for at least 10 years.²⁰

Until further work has established equivalence of glass and digital images, the glass slide should be considered the primary reference image which is retained for the patient record (i.e. the presence of a digital image does not substitute for retention of the glass slide).

Pathology departments should determine an appropriate retention policy for the digital images. While there remains a glass slide, this need not be prolonged. However, we recommend keeping the digital image for a period of two laboratory inspection cycles in case of any need to review it (e.g. for audit, quality control, medicolegal reasons).

5 Information technology considerations applicable to digital pathology

A deployment of digital pathology is a substantial information technology project. Pathologists should involve their local IT department for advice on planning and deployment of digital pathology, including plans for system backup, resilience and maintenance. In particular, consideration should be given to integration of laboratory information systems and digital pathology systems, and provision of appropriate information (e.g. clinical history, previous pathology reports) to assist pathologists in reporting on digital pathology systems. Interoperability between systems should also be considered – including interfaces between systems and interoperability standards where relevant (e.g. the DICOM standard for image transfer).

Pathologists may obtain advice on displays from their local medical physics or medical technology department. Some outline specifications for displays are provided below for reference.

6 Additional considerations for remote reporting (e.g. of intra-operative frozen sections)

In the past, robotic microscopes with remotely controlled stages have been used in telepathology systems for the remote reporting of intra-operative frozen sections in countries with geographically widely dispersed populations, such as Scandinavia and parts of North America. If a whole slide scanner can be installed at a satellite hospital then whole slide digital images are a feasible method of remotely reporting intra-operative frozen sections at hospitals which do not have a resident histopathologist. The general principles of validating/verifying such a system are the same as those for routine digital pathology, however, there are a number of other considerations when using digital pathology and telepathology in this role. Many of the points below will be relevant in other situations of remote reporting using digital pathology.

6.1 Cut-up of the specimen

The operative specimen should be cut-up by a trained biomedical scientist. Smaller specimens can be completely embedded for sectioning, while larger specimens require dissection and sampling. The reporting histopathologist needs to be certain that the correct areas have been sampled to detect malignancy. The best method for supervising the remote sampling of specimens may be to have a video camera above the cut-up board which streams live images to the remote histopathologist with a live audio connection enabling the biomedical scientist and histopathologist to discuss which areas should be sampled. If this is not feasible, standard specimen descriptions and/or photography are recommended.

6.2 Transmission of clinical details to the reporting histopathologist

The reporting histopathologist requires the same level of clinical information that they would have if reporting at the site of surgery. The clinical information on the request form may be sent by secure means to the remote histopathologist or the form may be digitally scanned and

sent by secure email to the histopathologist. The histopathologist should be in receipt of this copy of the request form before reporting the digital image.

6.3 Checking that the scanning equipment and electronic transmission is working

The main difference between using whole slide digital scanning for routine reporting and intra-operative frozen sections is that the latter are time-dependent and often mission-critical for the operating surgeon. Whole slide scanners are expensive items of equipment so it is likely that a satellite hospital will only have one scanner and any malfunction in the scanner will prevent the remote frozen section service being carried out. Although the hospital is likely to have a maintenance contract with the manufacturer of the scanner, all faults are very unlikely to be repaired in less than 24 hours. System checks are recommended on a regular basis to test the scanner, network and software. For example, at the start of each working day a slide is scanned and the image uploaded to the server that is used for frozen section reporting. The remote histopathologist can log into the system from the computer that they use for such reporting and check that they can access the scanned image. It is advisable to check that the video camera over the cut-up bench is working and producing a live stream of images – this can be done by leaving an item with moving parts, such as a clock with a second hand, on the cut-up bench.

6.4 Standard operating procedures for scanner malfunction

There should be clear standard operating procedures for instances when the scanner malfunctions. Some common causes of scanner malfunction, e.g. excess slide mountant, can be resolved by suitably trained biomedical scientists. If the fault in the scanner cannot be immediately repaired then other systems have to be ready for implementation which may include, if distances are relatively short, express courier of the specimen to the central hospital, or a histopathologist travelling to the satellite hospital. If these options are not practical, then the clinicians should be informed that the service is suspended.

6.5 Transmission of the report to the clinician.

The report will usually be transmitted verbally over the telephone in the same manner as most on-site frozen sections, with the usual precautions for ensuring accuracy of transmission.

7 Legal issues

Since digital pathology could be used to send images anywhere in the world for diagnosis, organisations should be aware of the legal issues that arise when a digital pathology service is delivered from outside national boundaries. Some of these issues are currently provided for by EU-wide directives. However, these would not apply where a non-EU country is involved.

7.1 Registration and revalidation

The registration of the reporting pathologist must be recognised by the regulatory body of the EU member state from which a hospital, health authority or other organisation purchases a remote digital pathology reporting service. This is an essential requirement in order to maintain proper standards of reporting. Reporting pathologists must demonstrate that they undergo appropriate continuing medical education and that they are properly trained for the tasks to be undertaken.

In the UK, the General Medical Council requires that doctors demonstrate their continued fitness to practise by the process of revalidation. It is essential that this process of assurance is also applied to those clinical pathologists providing digital pathology services from outside the UK.

7.2 Liability

Principles of duty of care are similar throughout the EU, and it is likely that in law any clinical pathologist who reviews images has this responsibility, whether the images are viewed using a microscope or a computer screen. In the National Health Service (NHS), it is the Trust that bears responsibility for patient care. In Scotland, this responsibility is borne by the Health Boards. Where harm to the patient occurs due to the negligence of a clinician employed or contracted by the Trust, then it is the Trust that bears vicarious responsibility for the acts or omissions of the clinician. However, it is important that in contracts between Trusts and suppliers of remote digital pathology, the liability of the supplier of the service and the reporting pathologist are clearly defined.

If the production of digital images is undertaken by a third party (e.g. a commercial imaging company), then the contractual agreement with that third party should make explicit the liability arising from the responsibility of the third party to produce digital images of (clearly defined) acceptable quality.

Duty of candour is now prescribed in Regulation 20 of the Care Quality Commission (March 2015) so digital pathology providers will have to inform patients when they became aware of a possible negligent act or omission.

7.3 Jurisdiction

Reporting that is carried out outside the UK does not affect the Trust's responsibility or potential liability to the patient. Moreover, a British patient who alleges that they have been harmed as a result of negligent reporting by a reporting pathologist practising within Europe, and who wishes to proceed against him or her directly, may issue proceedings either in the country in which the report was generated (known as the 'Primary Jurisdiction') or in the UK (the 'Alternative Jurisdiction'). Presumably the same is true of the reverse (i.e. where pathologists in the UK provide services for overseas institutions, they, or their employers, may be subject to legal proceedings in the patient's nation state).

A distinction may be made between the responsibility and liability for primary diagnostic reporting and the provision of advice by an expert pathologist on another site or in another country. Where expert opinion is being sought, the responsibility for accepting or rejecting that opinion and incorporating that opinion into a diagnostic report lies with the primary reporting pathologist.

7.4 Patient confidentiality

Any digital pathology service must ensure patient confidentiality. The technical specification must be sufficiently robust to ensure compliance with data protection and other privacy legislation. This is a complex area and expert advice on data protection compliance may be needed if patient-identifiable or potentially identifiable information is being transmitted, or if cloud-based storage is being considered. Information governance officers should be involved in the design of data protection arrangements. This is particularly so where pathologists are working at home or at other off-site locations.

7.5 Working Time Directive

The providers of the service must abide by EU health and safety legislation, including the Working Time Directive. If a distant pathologist is working in isolation, especially if remuneration is on the basis of a fee per specimen reported, there may be no way to ensure that excessive hours are not being worked, with consequent risk to reporting standards and patient safety.

8 General principles for validation and verification of digital pathology

Pathologists should ensure that the introduction of digital pathology is done safely, and that the service is not inferior to that provided prior to digitisation, with appropriate consideration of risks and clinical effectiveness as described in sections 3 to 8 above.

In the future, pathologists may practice fully digitally during training, as radiologists do. At that time, consultant pathologist training and validation in digital pathology may not be necessary or be very limited in scope. Laboratories will continue to be responsible for assessing the competence of their pathologists to comply with ISO 15189:2012.

As published evidence of safety and effectiveness increases, the validation and verification requirements for an individual institution or pathologist will become less onerous. Laboratories are still required to formally assess the commissioning of new equipment to establish it is performing to the expected standard (i.e. acceptance testing). Until that time, pathologists should take steps to ensure digital pathology is used safely and effectively.

Equipment verification should be undertaken prior to use. This should include important areas of performance such as slide scanning capacity, integration with laboratory information systems, barcode recognition, accuracy of tissue coverage, faint tissue detection, accuracy of image focus and resolution over a range of cases covering the laboratories workload. Checklists of identification of targets of interest form an important part of establishing scanner and viewing workstation performance is adequate for the proposed use.

For pathologist validation, where resources allow, a diagnostic accuracy study, designed to demonstrate non-inferiority, with diagnostic platform cross over and suitable washout can be performed.^{4,5,21} But this study design can be difficult to realise without sufficient financial resource, time, effort, and expertise in study design and analysis. It is not necessary to perform such a trial as part of a local validation.

Application of CAP guidelines has been cited by some pathologists as sufficient evidence for their own validation/verification in digital pathology. While they contain many useful suggestions and principles, we recommend a different approach to validation that has less impact on resources while being flexible and prioritising clinical safety.

Appendix A describes a suggested protocol to allow pathologists to train in, and self-validate with, digital pathology within a specified specialty or subspecialty. The protocol is designed to allow the pathologist to gain confidence in their digital diagnoses, while identifying challenging areas of digital diagnosis, which may require further training, experience, workflow modification or extra safety checks to ensure a secure diagnosis is rendered.

The validation process described has been successfully applied in one centre and the experience has been published.⁷

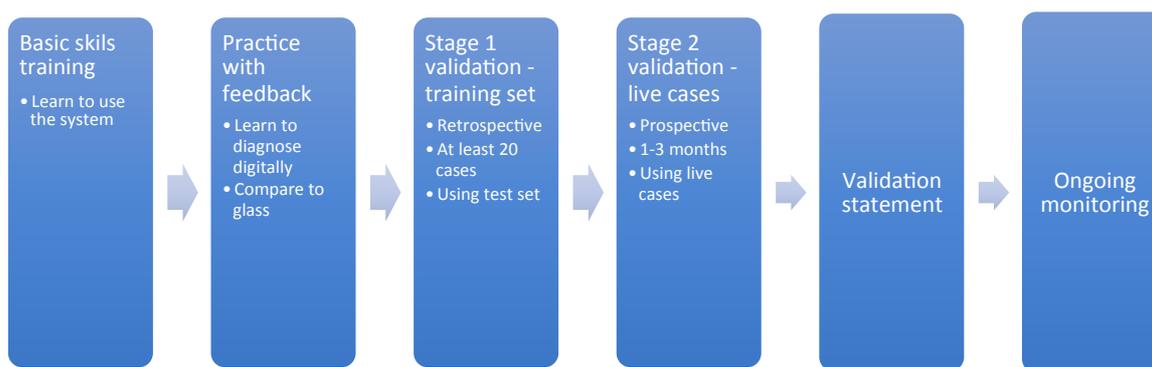
The guiding principles of this validation/verification approach are as follows.

8.1 Philosophy and approach

- Validation is a pathologist-led, self-validation process.
- While many cases are easily diagnosable using digital images, there are potential risks with digital diagnosis that must be identified and minimised.
- A recognition that although there is no evidence to suggest that digital pathology is unsafe, the published evidence is limited and of variable quality and its routine clinical use is relatively new. Therefore, a cautious approach, including ready recourse to conventional microscopes when needed, is appropriate.

- The validation should have sufficient rigor to satisfy a reasonable internal or external observer that safety and clinical effectiveness are maintained.
- Validation should include training both in the controls to use the system and the overall use of the system in context, including its strengths and weaknesses, so that pathologists are confident and knowledgeable users of digital pathology.
- Validation should occur in a real world context and be relevant to the proposed areas of practice.

The flowchart below gives an indication of an appropriate validation process, expanded in Appendix A.



8.2 Learning

Validation should have at its core a process of comparing digital diagnosis with glass diagnosis on the same cases, using the feedback loop to improve confidence and knowledge. The aim is not to measure the accuracy of reporting but to assess areas of difficulty when viewing slides digitally.

When comparing glass and digital diagnoses during the validation with live cases (stage 2), pathologists should use their discretion on how many slides to review. Initially they might review all slides for all cases on glass and digital, but as expertise and confidence increase, they may decide to review only index slides (i.e. those with the most important diagnostic features or difficult to read features).

Validation should be seen as a continuous learning and quality assurance activity rather than just seeking 'proof' of validation.

8.3 Duration and sample size necessary for validation

The duration of the validation and/or number of cases is not arbitrarily fixed by the College, as the validation will vary depending on the context and the individual pathologist.

A simple target for the duration of the validation or the number of cases to examine should be complementary to the development and assessment (through self-evaluation) of competence in digital diagnosis, which is the final goal.

The extent of validation should include a reasonable effort which would convince an external reviewer that reasonable evidence for safety and clinical effectiveness is established.

The duration and/or number of cases, and case mix of the validation should include (a) sufficient exposure to routine cases to gain confidence in routine and to (b) sufficient 'edge

cases', which are likely to be difficult on digital pathology to gain competence in them, and awareness of the limitations of the technology.

The case mix should also reflect the routine practice of the pathologist, so a "general" case mix reflecting their normal practice can be used for a general pathologist's workload; a mixture of specialist cases (e.g. breast, gastrointestinal cases) would be used for a specialist pathologist's workload.

A time-based approach may be more suitable than a numerical target. For example, one to three months of routine clinical practice is likely to convince an observer that reasonable efforts have been made to ensure safety. However, if validating in a low-volume speciality, it may be necessary to enrich the validation with more cases.

The pathologist will make more efficient use of time and resource by concentrating effort on learning from difficult cases, rather than pursuing a numerical target of cases.

In addition to comparison of diagnostic accuracy, validation should include assessment of objects that might be thought or predicted to cause problems on digital systems, such as dysplasia grading, weddellite calcification (calcium oxalate), mitotic figures, eosinophils, bacteria, viral inclusions, etc.

The validation should be extended in size or duration if deemed necessary during the process (e.g. to extend experience in one area, or to address problem areas).

8.4 Risk reduction

The pathologist should learn the difficulties and potential risks during the evaluation. The process should include risk reduction i.e. the development of strategies to reduce the risk of error in areas thought likely to present difficulties, such as grading of dysplasia, identification of bacteria and detection of small regions of diagnostic importance in large tissue sections.

These risk reduction strategies might include:

- deferral to glass slides when there is doubt on an individual case, or glass review for all slides in a particular area (e.g. some "fully digital" laboratories maintain glass review for sentinel lymph nodes)
- additional laboratory work (e.g. immunohistochemistry for small objects)
- getting a second opinion.

8.5 Quality assurance

Proper records should be kept of the validation and verification process including the training received, cases reviewed, results of glass-digital comparison and strategies developed. Ongoing monitoring of digital diagnosis should be included in laboratory quality assurance processes.

8.6 Repeat of validation/verification

A repeat validation will be necessary if significant changes are made to the whole slide imaging system.

A new validation/verification process will be necessary if a pathologist wishes to use digital pathology in a new area (e.g. a pathologist validated in breast pathology wishes to validate in skin pathology). As the pathologist has already learned skills in digital pathology and self-evaluation, a new validation could reasonably be more limited in scope and targeted to areas of problematic interpretation, and identification of objects of diagnostic importance.

An example validation process is shown in Appendix A, with supporting documents in Appendices B–E.

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10 References

- 1 William BJ, Bottoms D, Treanor D. Future-proofing pathology: the case for clinical adoption of digital pathology. *J Clin Pathol* 2017;70:1010–1018.
- 2 Electronic Code of Federal Regulations. *TITLE 21—Food and Drugs*. Accessed May 2017. Available from: https://www.ecfr.gov/cgi-bin/text-idx?SID=7fe8b0ef92a1bc872eec98d2812c9e22&mc=true&tpl=/ecfrbrowse/Title21/21cfrv1_02.t%20pl#0
- 3 Goacher E, Randell R, Williams B, Treanor D. The Diagnostic Concordance of Whole Slide Imaging and Light Microscopy: A Systematic Review. *Arch Pathol Lab Med* 2017;141:151–161.
- 4 Snead DR, Tsang Y-W, Meskiri A, Kimani PK, Crossman R, Rajpoot NM *et al*. Validation of digital pathology imaging for primary histopathological diagnosis. *Histopathology* 2016;68:1063–1072.
- 5 Mukhopadhyay S, Feldman MD, Abels E, Ashfaq R, Beltaifa S, Cacciabeve NG *et al*. Whole Slide Imaging Versus Microscopy for Primary Diagnosis in Surgical Pathology: A Multicenter Blinded Randomized Noninferiority Study of 1992 Cases (Pivotal Study). *Am J Surg Pathol* 2018;42:39–52.
- 6 Williams BJ, DaCosta P, Goacher E, Treanor D. A Systematic Analysis of Discordant Diagnoses in Digital Pathology Compared With Light Microscopy. *Arch of Pathol Lab* 2017;141:1712–1718.
- 7 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 on digital pathology validation and training. *Histopathology* 2017;DOI: 10.1111/his.13403 (Epub ahead of print).
- 8 Rashbass J, Furness P. *Telepathology: Guidance from the Royal College of Pathologists*. London, UK: The Royal College of Pathologists, 2005.
- 9 Lowe J, Trotter S. *Guidance for cellular pathologists on reporting at home (3rd edition)*. London, UK: The Royal College of Pathologists, 2005.
- 10 Pantanowitz L, Sinard JH, Henricks WH, Fatheree LA, Carter AB, Contis L *et al*. Validating whole slide imaging for diagnostic purposes in pathology: guideline from the College of American Pathologists Pathology and Laboratory Quality Center. *Arch Pathol Lab Med* 2013;137:1710–1722.
- 11 Hirschorn DS, Krupinski EA, Flynn MJ. PACS displays: how to select the right display technology. *J Am Coll Radiol* 2014;11:1270–1276.
- 12 Samei E, Badano A, Chakraborty D, Compton K, Cornelius C, Corrigan K *et al*. Assessment of display performance for medical imaging systems: executive summary of AAPM TG18 report. *Med Phys* 2005;32:1205–1225.
- 13 Brettelle DS. Display considerations for hospital-wide viewing of soft copy images. *Br J Radiol* 2007;80:503–507.
- 14 Norweck JT, Seibert JA, Andriole KP, Clunie DA, Curran BH, Flynn MJ *et al*. ACR–AAPM–SIIM technical standard for electronic practice of medical imaging. *J Digit Imaging* 2013;26:38–52.

- 15 US Food and Drug Administration Center for Devices and Radiological Health. *Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices Guidance for Industry and Food and Drug Administration Staff*. Silver Spring, MD, USA: US Food and Drug Administration, 2016.
- 16 Furness P. *Principles and guidance for interpretive external quality assessment schemes in laboratory medicine*. London, UK: The Royal College of Pathologists, 2017.
- 17 Fenton JJ. Is it time to stop paying for computer-aided mammography? *JAMA Intern Med* 2015;175:1837–1838.
- 18 Treanor D, Quirke P. The virtual slide and conventional microscope – a direct comparison of their diagnostic efficiency. *J Pathol* 2007;213:1A–65A.
- 19 Furness P. A randomized controlled trial of the diagnostic accuracy of internet-based telepathology compared with conventional microscopy. *Histopathology* 2007;50:266–273.
- 20 Wilkins B. *The retention and storage of pathological records and specimens (5th edition)*. London, UK: The Royal College of Pathologists, 2015.
- 21 Bauer TW, Schoenfield L, Slaw RJ, Yerian L, Sun Z, Henricks WH. Validation of whole slide imaging for primary diagnosis in surgical pathology. *Arch Pathol Lab Med* 2013;137:518–524.

Appendix A Example validation protocol for digital pathology

The following section presents one possible validation process, currently in use in Leeds, UK and Linköping, Sweden.

1 Validation protocol

The protocol represents a pragmatic approach to digital pathology deployment, minimising resource impact and clinical risk while maintaining diagnostic standards and patient safety. It allows conversion to digital practise relatively early in the procedure (stage 2), but with a “safety net” period of a mandatory check on glass. The protocol allows for prompt identification of diagnostic error in stage 2, when diagnoses are still rendered with reference to glass, and the subsequent development of workflow strategies to remove or minimise risk of further diagnostic errors.

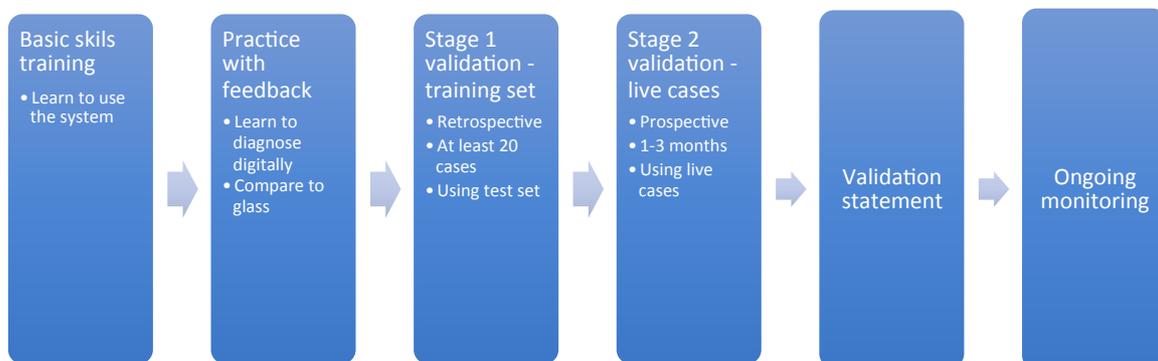
This protocol is not designed or powered to validate the accuracy of digital pathology itself in its own right (i.e. this does not replace the need for a clinical trial or regulatory approval).

This protocol is not intended or designed to judge the quality of pathology diagnosis or the competence of the pathologist.

Pathologists may discover additional issues as they undergo training and validation. In such cases the appropriate response of the pathologist may be greater awareness or a more careful approach in particular scenarios, a modification of protocols (e.g. performing additional levels or immunohistochemistry to assist with the detection of rare events) or reversion to the conventional microscope for certain cases.

1.1 Outline of suggested evaluation protocol

The flowchart below gives an outline of a suggested validation protocol.



1.2 Assumptions for validation

- Pathologists are experienced and competent in the diagnostic area being validated. While the protocol may provide a useful digital training experience for trainee pathologist, it is designed for fully trained pathologists, capable of independent sign out of cases from the diagnostic area being validated.
- A pathologist experienced in digital pathology is available as a trainer/facilitator
- Scanners undergo servicing and calibration according to the manufacturer guidelines, and relevant CE mark applications. Displays have been calibrated for brightness/contrast and ideally colour as well.

- The 'validation scope' is explicitly stated, to include the case types, stains, etc. included in the validation procedure. For example, 'breast pathology' or 'inflammatory skin pathology'.
- A training set for stage 1 validation is available and can be re-used in future re-validation studies – see below.
- Pathologists that complete validation for a particular subspecialty or topography will be required to complete a further validation procedure if they wish to report specimens from another subspecialty or topography not encompassed by their original validation scope. The second, and any subsequent validation procedure need not be as extensive as the primary validation, but should include a complete stage 1 (validation training set), to ensure confrontation with areas of known diagnostic difficulty.
- Dates of all training sessions completed by an individual will be documented.

2 Validation procedure

2.1 Basic skills training

The aim of this stage is to train the pathologist in the use of the system. It consists of a short (1 hour) training session in which the pathologist learns from an experienced user of the system (a trainer). Access to a help manual, workstation and test set are 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 as necessary
- how to access the documentation for the system
- how to identify gross scanning artefacts.

The pathologist reviews one to two cases on the digital system, with guidance and immediate feedback from the teacher about how to use the system.

2.2 Practice with feedback

The aim of this stage is to ensure that the pathologist is comfortable using the system. In their own time, the pathologist reviews a small test set of five to ten cases to familiarise themselves with the system.

At a review meeting with the trainer, the pathologist is observed while using the system to review one of the cases. Trainer and pathologist discuss the system, and any problems encountered.

2.3 Stage 1 validation – training set

The aim of this stage is to train the pathologist on the diagnostic appearances of cases using digital pathology. It will include exposure to cases anticipated to be challenging to diagnose digitally, and will encompass a variety of case types and stains as defined in the validation scope. A review of the literature pertinent to the validation scope should be used to identify cases and scenarios that are potentially difficult to diagnose on the digital platform.

A known set of slides is prepared, comprising a set number of cases – at least 20 cases – but this may be increased depending on the specialty and scope of the validation. These may be historic cases. Glass slides, digital slides and reports are made available to the pathologist.

The cases include a variety of examples including simple cases, complex cases and a variety of stains.

The pathologist reviews the training set, in their own time, over a short period of time (e.g. up to 2 weeks). For each case they make notes on the diagnosis on the digital slide. Then they immediately review the glass slides for the same case, and note their diagnosis. They make comments on the case on a proforma, including their diagnostic confidence using both the digital, and the glass slides for the case (see Appendix B).

At the end of the training set, the results are discussed at a small group training meeting. This should include discussion of the pitfalls noted in the test set, and explicit identification of the cases/features known to be difficult (e.g. grading of dysplasia or detection of micrometastases).

Once pathologist and trainer are both satisfied that the pathologist is familiar with the operation of the system and its use in the training cases, Stage 2 can proceed. If either the pathologist or trainer are not satisfied with the progress, stage 1 may be extended with more cases, or repeated, or a decision may be made to stop validation.

2.4 Stage 2 validation – live cases

During this stage the pathologist dual reports all of their cases using both digital and glass, to gain experience and confidence of using the technology.

All cases in the domain are scanned prospectively.

The sample size and duration of the validation can vary depending on the circumstances. The validation should be of sufficient length and detail so the pathologist develops proficiency and confidence in digital pathology – typically one to three months duration of the pathologist's normal practice. A typical sample should have with an appropriate mix of small biopsies and large resection cases, it should include routine cases and reflect some of the rarer and more challenging cases in the domain. All pathologists in this specialty should have a set minimum sample size or duration, agreed at the beginning of stage 2. The sample size or duration of the validation may be increased if the pathologist and/or trainer feel that this is necessary for that particular pathologist.

Cases should be scanned at a magnification appropriate for the clinical task being performed (e.g. immunohistochemistry may be assessed at 20x, but detailed cytological examinations may require 40x).

The pathologist reviews the entire case digitally first. They make their report using the usual method and write a short diagnosis on a spreadsheet/form.

The pathologist then reviews the glass slides immediately. They complete their report, making changes where necessary. A spreadsheet/form is provided for each pathologist (see Appendix C). For each case, the pathologist records the case number, their diagnostic confidence on both digital and glass (as a number on a Likert scale) and their preferred diagnostic modality, if any. If the case is deferred (digital slides not used for diagnosis), the reason for this should be recorded (e.g. image quality issue, workflow/timing issue). If the pathologist notes a discrepancy between their digital and glass assessment of the case, this should be documented. If the pathologist observes any differences in their perception of the case, short of factors altering diagnosis, they can comment on these in the comments box (e.g. Digital slide – nuclei looked very dark).

At the start of the validation procedure, it is likely that pathologists will review the majority of glass slides for each case, but as they gain experience and confidence, it is acceptable for the pathologist to review selected slides pertinent to the diagnosis only (e.g. the key diagnostic

slides or features in the case, or challenging slides/areas of slides). Where a pathologist has expressed low confidence in their digital diagnosis, a complete review of all glass slides would be expected.

The pathologist and trainer review the diagnosis spreadsheet after every 20% of the sample has been completed. If no major issues have arisen, the validation is continued. If issues are identified, they are addressed appropriately e.g. further training/modification of the validation set/exclusion of certain case types from the validation scope.

Throughout the validation process, cases identified as challenging to diagnose, or where pathologists have indicated differences in their glass/digital interpretations, should be shared and discussed within the department. In this way, a 'library' of problematic cases for a particular specialty can be assembled, which will provide a useful training and development resource for the department.

2.5 Validation statement and risk management

At the end of stage 2, the pathologist and trainer meet to discuss the validation results. Difficult cases, discrepancies and educational points are all discussed.

A document is produced (see Appendix D) that states:

- the training performed
- a summary of the glass-digital correlation overall in stage 2
- a list of any discrepancies noted in stage 1 and 2 with a comment on each
- percentage concordance rates between glass and digital diagnoses, expressed with non-excluded cases only, and with both excluded and non-excluded cases for stage 2
- the mutually agreed outcome of the validation, which is one of three options:
 - validated for full digital practice in the specified scope
 - validated for digital practice in certain areas, with reversion to glass for certain named exceptions
 - a decision not to proceed to digital diagnosis for this pathologist/validation set.

2.6 Ongoing quality control

Once a decision has been made to validate a pathologist for digital reporting in a particular scope, ongoing quality assurance procedures should be followed as part of clinical governance.

These might include:

- 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
- audit protocols should be introduced to allow random review of a proportion of an individual pathologist's digital cases on a rolling basis.

Appendix B Stage 1 training record

SAMPLE – STAGE 1 TRAINING CASE RECORD SHEET

Breast Test Set

Case 1 (3 slides)

Specimen type - Left breast lump

Clinical details - Diagnostic excision biopsy. Left breast 12 o'clock. Elective excision U2 C2 fibroadenoma.

Macro - Lump of fibrofatty breast parenchyma which weighs 10.1g and measures 35x24x20mm. 3 representative pieces.

Digital diagnosis

How would you rate your confidence in your diagnosis?

1	2	3	4	5	6	7
Not confident At all						Very Confident

Glass diagnosis - has your impression of the case changed?

How would you rate your confidence in your glass diagnosis?

1	2	3	4	5	6	7
Not confident At all						Very Confident

Comments

Appendix C Stage 2 validation record

Date	Case no.	Digital diagnosis	Glass diagnosis (if different)	Confidence in digital diagnosis (1-7)	Confidence in glass diagnosis (1-7)	Preferred method of diagnosis (d=digital, g=glass, n=neither)	Discrepancy/ deferral	Comment

Appendix D Validation summary and outcome record

VALIDATION SUMMARY

Pathologist: _____

Specialty: _____

Trainer: _____

1. Summary of training:

Date	Description

2. Summary of diagnostic concordance:

	No. of cases	% concordance	% deferrals
Validation Stage 1: Training Set			
Validation Stage 2: Live cases, including deferred cases			
Validation Stage 2: Live cases, excluding deferred cases			

3. Summary of discordances:

Validation Stage	Digital Diagnosis	Glass Diagnosis	Comments

4. Record of meetings with trainer/validation group:

Date	Comments

5. Other comments. The pathologist or trainer may use this space to record any concerns or observations they wish to raise regarding their use of digital pathology for primary diagnosis.

VALIDATION OUTCOME

Pathologist: _____

Specialty: _____

Trainer: _____

The pathologist has completed a course of digital pathology training and validation procedure. As a result of discussion between the pathologist and trainer, the mutually agreed outcome of this validation procedure is:

1. fully validated for digital primary diagnosis in the specified diagnostic area
2. validated for digital primary diagnosis in the specified diagnostic area, with some exceptions/workflow modifications (see below)
3. not validated for digital primary diagnosis in the specified diagnostic area at this time.

For outcome 2, please describe exceptions/modifications below:

Signatures:

Pathologist _____

Trainer _____

Date _____

Appendix E Example validation sets for breast pathology

Dr Bethany Williams, November 2016

- The test set should include exposure to locally relevant specimens, tissues and immunostains, to ensure the pathologist is comfortable performing a range of tasks, and viewing a range of stains.
- Immediate check of validation cases on glass will allow pathologist to directly compare appearance of stains/nuclei, etc on the two platforms.
- Some of the cases will be challenging, but are designed to prompt discussion and consideration of workflows e.g. deferral to glass, deferral to immunos.

1 Scope of test slides

1.1 Specimen type

- Core biopsies
- Mammotome biopsies
- Diagnostic excision specimens
- Therapeutic excision specimens

1.2 Tissue type

- Nipple
- Breast
- Lymph node

1.3 Stains

- H&E
- Ck/myoepithelial markers
- ER/PR immuno
- Her2 immuno

1.4 Diagnoses

- Benign breast disease/inflammatory conditions
- Calcification (need to check glass for weddelite)
- Epithelial atypia
- In situ carcinoma
- Invasive carcinoma incl. identification of special types
- Benign fibroepithelial lesions
- Malignant fibroepithelial lesions

1.5 Tasks

- Diagnosis
- Grading incl. mitotic count and nuclear assessment
- Identification of microinvasion/LVSI
- Identification of calcium in screening specimens
- Interpretation of immunostains incl. Her2, PR
- Interpretation of myoepithelial/ck immunos
- Identification of micrometastases

2 Potential pitfalls

- Recognising epithelial atypia
- Identifying microinvasion/LVSI
- Identification of micrometastases
- Identification of calcium (weddelite)
- Granulomatous inflammation
- Lobular carcinoma

Appendix F Example validation sets for lung pathology

Dr Bethany Williams, November 2016

- The test set should include exposure to locally relevant specimens, tissues and immunostains, to ensure the pathologist is comfortable performing a range of tasks, and viewing a range of stains.
- Immediate check of validation cases on glass will allow pathologist to directly compare appearance of stains/nuclei, etc on the two platforms.
- Some of the cases will be challenging, but are designed to prompt discussion and consideration of workflows e.g. deferral to glass, deferral to immunos.

1 Scope of test slides

1.1 Specimen type (may not be necessary to include whole cases – could scan selected slides)

- Needle biopsies (including EBUS of bronchus/lymph nodes)
- Diagnostic excision specimens (including wedge biopsies for interstitial disease)
- Therapeutic excision specimens (partial and total pneumonectomy)
- Pleural biopsies/resections

1.2 Tissue type

- Lung
- Pleura
- Lymph node

1.3 Stains

- H&E
- Squamous markers
- Adenocarcinoma markers/mucin stains
- Neuroendocrine markers
- Mesothelial markers
- ZN, fungal stains
- Elastin stains

1.4 Diagnostic categories

- Interstitial lung disease patterns (acute lung injury, fibrosis, chronic cellular interstitial infiltrates, alveolar filling, nodules)
- Vasculitides
- Granulomatous disease
- Mycobacteria

- Fungal infection
- Asbestosis/pneumoconiosis
- Lymphoproliferative disease
- Small cell carcinoma
- Non-small-cell carcinomas
- Mesothelioma
- Sarcoma
- Lymph nodes (NAD/reactive, sarcoid/other granulomatous disease and positive for metastatic malignancy)

1.5 Tasks

- Diagnosis – interstitial lung disease
- Diagnosis – granulomatous disease/mycobacteria
- Diagnosis – malignancy
- Diagnosis – metastatic tumour in lymph nodes
- Tumour typing – small cell v non-small-cell, adeno v squamous, mesothelial, etc
- Tumour grading
- Identification of microorganisms
- Interpretation of immunostains incl. mesothelial/epithelial markers
- Interpretation of special stains e.g. ZN, fungal stains, elastin

2 Potential pitfalls

- Dysplasia/malignancy recognition on small biopsies
- Micro-organisms
- Granulomatous inflammation
- Micrometastasis/malignant cells in lymph node EBUS
- Identification/classification of granulocytes in interstitial lung disease

Appendix G AGREE II compliance monitoring sheet

AGREE standard	Section of document
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Section 1
2 The health question(s) covered by the guideline is (are) specifically described	Section 1.2 and 1.3
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Section 1.2 and 1.3
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Yes, following the normal College consultation procedures
6 The target users of the guideline are clearly defined	Section 1.2
Rigour of development	
7 Systematic methods were used to search for evidence	Section 2.4, 2.5
8 The criteria for selecting the evidence are clearly described	Section 2.4
9 The strengths and limitations of the body of evidence are clearly described	Section 2.4–2.7 and section 3
10 The methods for formulating the recommendations are clearly described	Section 2.2 to 2.7 and section 3
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Section 2 and 3
12 There is an explicit link between the recommendations and the supporting evidence	Section 2.2 to 2.7 and section 3
13 The guideline has been externally reviewed by experts prior to its publication	Yes, following normal College consultation procedures
14 A procedure for updating the guideline is provided	Section 1.4
Clarity of presentation	
15 The recommendations are specific and unambiguous	Specific recommendations are included
16 The different options for management of the condition or health issue are clearly presented	Not directly relevant – deferral to light microscopy is suggested where necessary
17 Key recommendations are easily identifiable	Section 8.1
Applicability	
18 The guideline describes facilitators and barriers to its application	Section 2–8
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Section 8 and Appendices A–F
20 The potential resource implications of applying the recommendations have been considered	The resource implications are not directly relevant since these are best practice

	recommendations for using digital pathology rather than the cost-benefit analysis of implementing it. Nevertheless, the recommendations contain information about how the relevant resource needs could be assessed.
21 The guideline presents monitoring and/or auditing criteria	Section 8.5-8.6
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Yes. Relevant disclosures have been provided.
23 Competing interest of guideline development group members have been recorded and addressed	Yes