Commissioning Brief - Supporting Information

Whole slide imaging in pathology

Closing date: 30 November 2017

This supporting document provides further information to support applicants for this call. It is intended to summarize what prompted the call and the existing evidence base, including relevant work from the HTA and wider NIHR research portfolio. It was researched and written on the basis of information from a search of relevant sources and databases, and in consultation with a number of experts in the field. Searches and information provided were up to date as of April 2017.

Source of topic: National Screening Committee

Patient group

Pathology services play an important role in the NHS including in NHS screening and monitoring services. [1]

Approximately 800 million tests are performed annually (14 for each person in England and Wales) with 300,000 patients having a test each working day.[1] Increasing demands for tests and diagnoses, with the changing demography of the UK are putting ever increasing pressure on pathology services. [2]

The National Pathology Programme’s Digital First report [1] highlights the potential that digital innovations and efficiencies could make across the NHS. While digital transfer of data/patient records is now common place, the digitalisation of diagnostic pathology services will take much longer to implement, and more evidence is still required to show digital workflows are at least as safe and efficient as traditional techniques.

There are considerable opportunities to benefit from the use of digital pathology in some situations, e.g. to ameliorate a shortage of pathologists, to access a specialised service, to obtain a rapid second opinion or its use in quality assurance.

NICE and other guidance

There are no NICE guidelines relevant to this present topic but the Royal College of Pathologists has recently completed a Digital Pathology Guideline (publication imminent).

The guidelines 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 base the guidelines on published evidence, including the only registered published systematic review of the literature [6, below], and personal experience of using and developing digital pathology systems.

Current practice and proposed intervention

Diagnoses requiring the use of microscopy (whether it be of tissue, blood or other samples) has been done using light microscopy on mounted glass slides (glass slide microscopy (GSM) i.e. a pathologist looking down a microscope, moving the slide about to find areas of interest and make a diagnosis).
Modern technology allows the high resolution imaging of glass slides (at various magnifications) so that digital images can be viewed retrospectively (i.e. without the need for the source slide to be present) and thus allows images to be shared. This does mean however that the pathologist must rely on the quality of the captured image (and of the viewing system being used) as they potentially do not have the original slide available to check against. Because very high resolution images (at the highest magnifications) are also required the file sizes of images are also very large, which necessitates modern, high power and fast processing equipment and data transfer facilities.

Digital pathology/whole slide imaging (WSI) is gaining growing interest as a means to maximise efficiencies and modernise pathology with several UK centres (e.g. Leeds, Sheffield, Coventry and Warwickshire) already moving towards integrating digital workflows for their pathology services. In Europe, some WSI instruments have regulatory approval for diagnostic use (CE Mark) and in the US the FDA has just given its first regulatory approval for WSI for diagnosis although various vendors are preparing FDA submissions.

Queen’s University Belfast was recently awarded one of five Cancer Research UK (CRUK) Centres Network Accelerator Awards to lead a five centre collaboration to establish a national digital pathology and image analysis platform for solid tumours (with the University of Southampton, University College London, University of Manchester, University of Newcastle and University of Leicester).

The University of Leeds has a Virtual Pathology website which includes a searchable database of over 6,000 slide specimens which are viewable within a fully interactive slide viewer, with many of the slides being annotated to show regions of interest. Leeds also hosts several digital EQA schemes, including the mandatory digital EQA scheme run for the English Bowel cancer screening programme.

A number of recent narrative reviews/commentaries helpfully set out the current situation and what further work needs to be done before wide spread implementation is likely [3,4,5]

Although the technology exists, and is continually being developed, it is still accepted that a definitive adequately powered validation study is still required in order to fully substantiate previous indications of concordance between WSI and GSM so that wider adoption of digital pathology is possible.

Cost and implications for NHS spend

The initial capital investment as well as ongoing costs in digital pathology systems is undeniably significant but the possible efficiency gains are likely to be cost-saving, even in the short term. For example Griffin & Treanor et al [3], in their recent narrative review, estimate an initial outlay of approximately £1.4M, with ongoing costs of £250k per year. Using data from the author's institution they completed a simple cost–benefit analysis to show the time taken for a return on investment. The institution, a large teaching hospital department comprising 45 full-time equivalent consultant pathologists and 120 laboratory and administration staff processes 80k specimens per year. With improvements in productivity of 10% or 15%, their model showed break even at years 2 or 1, respectively. A department half this size with a productivity improvement of 10% should achieve this after 4 years. The authors also note that improvement in efficiency of 5% would never recoup the initial investment, though there may be other benefits to the organisation.

As with most new technologies it is likely that the cost of equipment will reduce over time and training and other costs might also reduce as digital pathology becomes much more routine.

Completed research

Evidence Synthesis

The most up to date and comprehensive systematic review [6] has shown some evidence for the accuracy of WSI but the overall quality of evidence is poor with most studies being small and of varying quality. The review, with searches completed to March 2015 included 38 studies. They found the mean diagnostic concordance of WSI and LM, weighted by the number of cases per study, was 92.4%. Of the 30 studies quoting percentage concordance, 18 (60%) showed a concordance of 90% or greater, of which 10 (33%) showed a concordance of 95% or greater. The authors concluded that further validation studies are still needed.

The Leeds group (authors of the review above) have also recently completed a systematic review [7] utilising the protocol from the review above but to investigate discordance in WSI. This review includes 23 studies yielding 8069 comparisons between glass and digital diagnosis with 335 instances of
discordance of which only 28 discordances had the potential to cause moderate or major patient harm. The authors identified a number of problem areas in digital diagnosis, which 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.

**Primary Research**

  The largest published study to date. Seventeen pathologists re-reported 3017 cases by digital pathology. Of these, 1009 were re-reported by the same pathologist, and 2008 by a different pathologist. Re-examination of 10, 138 scanned slides produced 72 variances between glass slide and digital pathology reports, including 21 clinically significant variances, the authors noting that these results are within the 95% confidence interval for existing intraobserver and interobserver variability, and proving that digital pathology is non-inferior to glass slide microscopy.

- Shah et al (2016). *Validation of diagnostic accuracy with whole-slide imaging compared with glass slide review in dermatopathology.* [9]
  A comprehensive retrospective WSI validation study of routine dermatopathology cases, adhering to College of American Pathologists (telepathology validation guidelines. 181 consecutive cases arranged into 3 categories (inflammatory, melanocytic, nonmelanocytic proliferations) were reviewed by 3 board-certified dermatopathologists via GSM and WSI. Intraobserver and interobserver diagnostic concordance between WSI and GSM was equivalent. The authors concluded that WSI appears to be a reliable diagnostic modality for dermatopathology.

  Pathologists were randomized to interpret one of four sets of breast biopsy cases during two phases, separated by ≥9 months, using GSM or WSI (sixty cases per set, one slide per case, n = 240 cases). 252 pathologists consented to randomization with 208 completing Phase I (115 glass, 93 digital) and 172 completing Phase II (86 glass, 86 digital). Accuracy was slightly higher using glass compared to digital format and varied by category: invasive carcinoma, 96% versus 93% (P = 0.04); ductal carcinoma in situ (DCIS), 84% versus 79% (P < 0.01); atypia, 48% versus 43% (P = 0.08); and benign without atypia, 87% versus 82% (P < 0.01). There was a small decrease in intraobserver agreement when the format changed compared to when glass slides were used in both phases (P = 0.08). The authors concluded that digital format interpretations were similar to glass slide interpretations of benign and invasive cancer cases. However, cases in the middle of the spectrum, where more inherent variability exists, may be more problematic in digital format.

**Research in progress**

**Evidence Synthesis**

Nothing relevant identified.

**Primary Research**

The EU funded FP7 AIDPATH ‘Academia and Industry Collaboration for Digital Pathology’ 3M Euro project (4 years to Oct 2017) is a pan European collaboration (including Loughborough and Nottingham Universities) which aims to develop efficient and innovative products to fulfill the needs of digital pathology. The project has four work packages:

- WP1: Optimizing, calibrating and standardizing digital pathology image display.
- WP2: Advances image analysis for whole slide images.
- WP3: Evaluation and quantification of biomarkers.
- WP4: Clinical evaluation of the processing tools.

A small number of industry funded validation studies (of their own systems) were identified which have just completed, or should have completed, but no results relating to these could be found:
Two studies by Philips: NCT02699970 and NCT02529137
- One from Omnyx: NCT02470572

In addition there are a small number of projects looking at developing algorithms for machine readable detection of histopathological abnormalities but these are out with remit of this current brief.

NIHR Evaluation, Trials and Studies Research
Nothing relevant identified.

References