Randell R, Ruddle R, Thomas R, Treanor D. (2012) Diagnosis at the microscope: a workplace study of histopathology. Cognition, Technology & Work 14(4) pp.319-335
The final publication is available at www.springerlink.com

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Title: Diagnosis at the microscope: A workplace study of histopathology

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Abstract
Histopathologists diagnose cancer and other diseases by using a microscope to examine glass slides containing thin sections of human tissue. Technological advances mean that it is now possible to digitise the slides so that they can be viewed on a computer, promising a number of benefits in terms of both efficiency and safety. Despite this, uptake of digital microscopy for diagnostic work has been slow and research suggests scepticism and uncertainty amongst histopathologists. In order to design a successful digital microscope, one which fits with the work practices of histopathologists and which they are happy to use within their daily work, we have undertaken a workplace study of a histopathology department. In this paper, we present the findings of that study and discuss the implications of these findings for the design of a digital microscope. The findings emphasise the way in which a diagnosis is built up as particular features on the glass slides are noticed and highlighted and the various information sources that are drawn on in the process of making a diagnosis.

Keywords: Healthcare; Histopathology; Digital pathology; Workplace study

1. Introduction

Histopathologists diagnose cancer and other diseases by using a microscope to examine glass slides containing thin sections of human tissue. Technological advances mean that it is now possible to digitise the slides so that they can be viewed on a computer. Digital pathology promises a number of benefits, both in terms of efficiency and safety. Advocates of digital pathology highlight the potential for improved workflow; a digital system would allow the histopathologist to be alerted to when new cases are ready to be viewed, as well as allowing the pooling of cases, resulting in a revolution of the workflow similar to that seen in radiology (Gilbertson et al. 2006). There is also the ease of obtaining second opinions electronically from a national or international source rather than having to send the glass slides through the post with the delay and the risk that they will get broken or lost in transit (Della Mea et al. 2006). Slides can be simultaneously sent to several people for second opinions, not possible with glass slides. There is the reduced risk of getting slides mixed up so that a patient receives the wrong diagnosis, something that happens rarely but can have devastating consequences when it does (Nakhleh 2008), and there is the option to integrate decision support technology.

Despite this potential, uptake of digital microscopy for diagnostic work has been slow. While there have been positive reports about the use of digital microscopy within education and training (Blake et al. 2003; Kumar et al. 2004), in relation to diagnostic work, research suggests scepticism and uncertainty amongst histopathologists (Dennis et al. 2005). In order to design a successful digital microscope for diagnostic pathology – one which fits with the work practices of histopathologists, which they are happy to use within their daily work – we need an understanding of their current work practices and the context within which they carry out their work. To the outside world, including other hospital departments and hospital management, the histopathology department often appears to function as a black box (Meijer et al., 2009). Therefore, we have undertaken observations that explicate the detail of how histopathologists accomplish their work, in order to produce an account of work practices in histopathology.

In the following section, we describe the current technology of histopathology, in terms of the creation of glass slides and the conventional light microscopes that are used to view them, and then consider previous studies of the work of histopathologists. We then describe the methods used for this study, as well as explaining the motivation behind the choice of methods. We then present the findings, describing the activities involved in coming to a diagnosis and the artefacts that are used in support of this. In the discussion, we explore the implications of our findings for the design of a digital microscope.

2. Background

2.1 Producing the glass slides

Histopathology slides are produced by a complex process involving significant amounts of manual activities and information processing. For each patient, the histopathology laboratory will receive one specimen, which may consist of multiple parts (e.g. from the stomach and the duodenum), and these range from tiny pieces of tissue taken in a biopsy up to one or more entire organs. The first step in the process of producing glass slides is known as specimen dissection, ‘cut up’ (UK) or grossing (USA). In this step, larger specimens are examined macroscopically for the presence of disease, and tissue pieces taken. Smaller parts are sampled in their entirety,

sometimes without being re-examined grossly. So-called tissue cassettes containing these tissue pieces are then processed chemically to 'fix' the tissue. It is then embedded in a small block of paraffin to mount it for sectioning. Thin (5 µm) sections are then cut from the tissue block using a specialised microtome and the sections placed on standard (75 x 25mm) glass slides. Several sections may be taken from a block. These are referred to as 'levels' and typically three levels are used. All sections may be placed on a single slide, ordered sequentially, or they may be placed on several slides. These can then be stained with a variety of chemical or immunologically based methods. The commonest method, which highlights most significant tissue structures well, is a so-called haematoxylin and eosin method (H&E). Special stains, which use histochemical reactions to identify specific tissue components or organisms that are less easily identifiable with an H&E stain, are not routine and are usually requested by the histopathologist once they have viewed the H&E slides. Similarly, immunohistochemcial stains ('immunostains' or IHCs), which target specific antigens on a cell using specific antibodies, are used to confirm the presence or absence of that protein. These are usually requested by the histopathologist once they have viewed the H&E slides.

A variation of this process is carried out for intraoperative consultations where 'frozen section' slides are produced. The tissue is frozen rather than being processed in the way described above, allowing for rapid microscopic examination of the tissue. Frozen section slides are typically stained with H&E but the quality of the slides produced by frozen section is lower than slides produced through paraffin embedding. Therefore, following the histopathologist's examination of the frozen section slides, standard H&E slides will be produced.

Each slide will have a label, which typically gives the name of the hospital or organisation where the slide was produced, the accession number which is a unique identifier given to each specimen that arrives in the lab, a number or letter signifying the part, the patient name, the stain that has been used (e.g. H&E) and, where relevant, the number of levels. For example, if six levels are taken and placed over two slides, the first slide will say 'L1-3' and the second slide will say 'L4-6'. Some hospitals also add barcodes to the slides to encode this data.

2.2 The conventional microscope

The conventional light microscope has a mechanical 'stage', on which the glass slide is placed, with stage clips that hold the slide in place. The stage control, just below the stage, allows the user to make small movements to adjust which part of the slide they are viewing. A light source below the stage is used to sample the image. A number of objective lenses provide different levels of magnification, with most microscopes having lenses that range from 2.5x to 40x magnification. The eyepieces on the microscope also magnify the image by a further factor of 10, so the final magnification applied using a 20x lens is actually 200x. However by convention this additional factor of magnification is not included when histopathologists describe what magnification they are reviewing tissue at.

Fig. 1: The conventional microscope

2.3 Previous studies of histopathology

Within histopathology, there have been studies of the work of histopathologists for the purpose of supporting workload allocation and increasing efficiency and these provide some initial insights into the work that takes place and the factors that impact on the work. Clark and Chomyn (2010) describe the factors that affect how many cases a histopathologist can report in a day, including: variation in the time to report a case due to its complexity; the experience, training and degree of sub-specialist expertise of the individual histopathologist; variation in the time available to report cases within the working day due to other activities such as multidisciplinary team (MDT) meetings, autopsies, dealing with enquiries from clinicians; the quality and reliability of the laboratory IT system; and the efficiency of the laboratory. Meijer et al (2009) describe how the histopathologists' workload has increased in recent years due to an aging population with more possible cancer patients (and therefore an increase in the number of presented specimens), an increasing number of diagnostic procedures available to the clinician that allow for taking biopsies, such as new endoscopic techniques, and advances in biomedical science such as targeted oncology therapies that require additional diagnostic procedures such as immunohistochemistry and lead to increasingly complex diagnostic reports.

There is also a body of research that has considered the process through which histopathologists examine a slide. For example, Crowley et al. (2003), using information processing as a theoretical framework, studied the diagnostic processes of pathologists by attaching cameras to participants' microscopes and combining this with the think-aloud technique. The transcripts were coded to capture different processes. These codes were then used to produce quantitative data regarding the frequency of such processes (or at least the frequency with which participants verbalised behaviours that could be characterised as reflecting these processes). The categories of processes included data examination (visual identification, visual comparison and examination of history), data exploration and explanation, and data interpretation.

A number of studies have looked at the diagnostic track of histopathologists as they look at a slide. These studies have identified different patterns, such as a 'scanning style' and a 'selective style' (Tiersma et al. 2003), as well as highlighting differences in the behaviour of expert histopathologists and trainees (Krupinski et al. 2006; Treanor et al. 2009).

What is not provided by existing studies of the work of histopathologists is an understanding of the work of diagnosis within its real-world context. For example, microscopy imagery is interpreted by the histopathologist in the context of clinical and sample information (Hamilton et al. 2009) and diagnoses are made within the context of grading and classification systems (Fandel et al. 2008). Diagnostic work does not necessarily begin and end at the microscope. Rather, it may begin at the histopathologist's first contact with the specimen and does not end until the histopathologist has translated what is viewed on the slide into a written assessment. It is this gap in the literature that this research hopes to address.

3. Methods

Within the fields of Human-Computer Interaction (HCI) and Computer Supported Cooperative Work (CSCW), there is a growing body of studies that seek to capture the details of work practice within particular settings through the use of naturalistic observations (Heath and Luff 2000; Luff et al. 2000). The motivation for the use of such workplace studies comes from recognition that rejection of systems by their intended users typically results from lack of attention to the social context of work practice (Forsythe 1999). Influenced by such work, we undertook a workplace study in a histopathology department within a large UK teaching hospital.

3.1 The setting

Leeds Teaching Hospitals NHS Trust Histopathology department is the biggest single site Histopathology department in the UK. It has 39 full-time equivalent consultant histopathologist staff, approximately 30 trainee medical histopathologist staff, and approximately 150 laboratory staff. The Department reports all histopathology subspecialties including neuropathology and paediatric pathology as well as providing a cytology and autopsy service. The Department processes approximately 58,000 surgical specimen parts per year, producing approximately 250,000 glass slides.

Histopathologists in the Department work in a highly specialised manner, with most working in one or two subspecialties. This is a model seen in many larger hospitals; smaller hospitals tend to have less subspecialisation with histopathologists reporting a broader spectrum of work.

For primary diagnosis the Department receives specimens from Leeds Teaching Hospitals Trust as well as from the primary care practices in the surrounding area. The Department provides a secondary and tertiary referral service for many subspecialties. In 2009 it reported nearly 800 second opinion cases and 1300 cases referred to Leeds for MDT meetings.

3.2 Data collection

Observations of ten consultant histopathologists, with a variety of subspecialties (breast, cardiothoracic, gastrointestinal, liver, lung, renal, skin and soft tissue, and urology) were undertaken. The researcher sat with the histopathologist in their office as they undertook their routine work. Nine of the ten histopathologists had a double headed microscope, enabling the researcher to observe what they were looking at on the slide. Each observation session lasted approximately one hour. Photographs of locations and artefacts were taken.

Fieldnotes captured not only what happened but also the context in which it happened, describing the locations in which the work took place and the artefacts that were used to support that work. While the histopathologists were not asked to 'think aloud' during the observations, eight of the histopathologists did describe what they were doing, although there was much variation in the level of detail. One of the histopathologists viewed the slides in the way that he normally would, not providing any description, but afterwards talked the researcher through what he had noticed on the slides and what he had recorded in the report. The sessions were audio recorded, in order to capture the histopathologists' comments and descriptions of their work.

In addition, we also observed one cut-up session, two MDT meetings, two sessions where histopathologists together reviewed slides in preparation for an MDT meeting, and one teaching session for trainee histopathologists, in order to understand the histopathologists' work in its broader context. The observations were undertaken between December 2009 and August 2010.

Local Research Ethics Committee approval for this research was obtained and written consent was gained from all participants.

3.3 Analysis

Following data collection, the audio recordings of the observation sessions were transcribed, although no patient identifiable data was transcribed. These transcripts were then annotated with the fieldnotes, with all staff names replaced with a unique identifier, e.g. CH1 for Consultant Histopathologist 1. The annotated transcripts were then entered into NVivo for analysis. Before beginning indexing of the data, all fieldnotes were carefully read and annotated by hand, asking questions of the data and paying attention to what was occurring and in what order, what was being accomplished and what strategies were used to achieve this (Emerson et al. 1995). From this, a series of codes were developed to index details of the process and the context and the various strategies identified in the accomplishment of the work. Indexing was treated as a way of engaging with the data on a line by line basis.

4. Findings

For readability, we have broken up the description of the work of the histopathologists into a number of sequential phases. The histopathologist receives a number of cases, collecting them from his pigeon hole, and before viewing the slides he arranges the cases in order according to urgency and other factors (Section 4.1). The histopathologist then looks at the clinical details for the patient (Section 4.2), before moving on to view the slides (Section 4.3). They may compare slides (Section 4.3.1), request additional slides (Section 4.3.2) or ask for

a colleague's opinion on the case (Section 4.3.3), before producing a report for the case (Section 4.4). Figure 2 provides a graphical representation of this process. In reality these phases often overlap (e.g. dictating a report while viewing the slides) or are subsequently returned to (e.g. looking again at the clinical details after viewing the slides), as will become apparent.

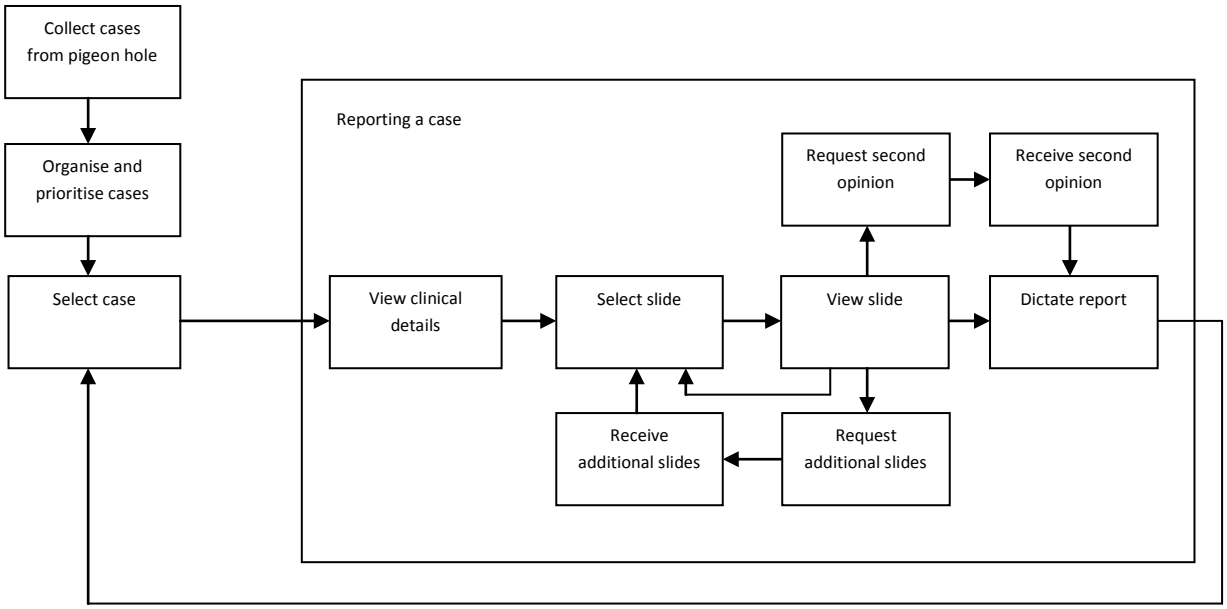

Fig. 2: Overview of the process of reporting a case

It is also worth noting the potential for interruptions to these phases; a total of sixteen interruptions were recorded over the observation sessions, predominantly telephone calls (8) or trainees or colleagues asking for second opinions (7), with one histopathologist experiencing four interruptions within the one hour of observation.

4.1 Receiving and organising cases

Histopathologists typically collect cases that have been allocated to them from their pigeon hole. Urgent cases may be brought to them by a member of the lab staff. Additionally, they may receive cases from colleagues requesting a second opinion. For some specialties, a 'pool' system operates, where whoever is allocated to monitor the pool routinely checks the appropriate space in the lab for any new cases that have come in and takes as many cases as they feel they can report.

A case consists of between one and one hundred and fifty slides, placed in cardboard trays, and the relevant paperwork (described in the following section). Most slides will be H&E stains, although for particular types of cases, slides with certain special stains will automatically be produced by the laboratory staff. For each special stain (i.e. any stain other than an H&E), a control slide is produced, so that the histopathologist can check that the stain has worked. This may or may not be included in the tray, depending on how many cases it acted as the control for.

The cases in the histopathologist's pigeon hole will not be in any particular order. Therefore, having collected a pile of cases from their pigeon hole, most histopathologists will arrange the cases in order. Various criteria are used to order cases, including the level of urgency already assigned to the case, whether or not the case already has a diagnosis, and the histopathologist's preferred pattern of working. We describe these criteria further below.

At Leeds some cases are marked with stickers to show that it is urgent – the requesting clinician will put a green sticker on the request form but, as this might not be seen in a pile of cases, the lab staff attach an additional red sticker on the top of the form so that it sticks out from the pile of cases. These cases will typically be viewed first. (The exception to this is in particular specialties where all cases are classed as urgent as with, for example, breast cancer screening).

Histopathologists also distinguish between those cases which are 'a new diagnosis' (the patient does not yet have a diagnosis) and those which are not (the patient already has a diagnosis). Histopathologists are involved not only in the initial diagnosis (confirming a clinically suspected diagnosis, or making a new diagnosis which was not expected clinically) but also in monitoring a known diagnosis or response to treatment, for example, assessing the success of chemotherapy or, following surgery, determining if the surgeon has removed all of the tumour. Those cases where the patient has not yet received a diagnosis may be treated as being more urgent, on the basis that treatment cannot start until a diagnosis has been given.

In addition, histopathologists may order the cases according to their preferred working pattern, for example, doing the more complex cases first while still feeling fresh and leaving what they perceive to be more 'straightforward' cases to the afternoon. They may also choose to group cases, for example, viewing all liver biopsies together.

When organising the cases, it is also necessary to match up newly arrived slides with those cases that are already in the histopathologist's office. This 'glass work' occurs when an 'extra work request' (described further in Section 4.3.2) has been issued, requesting either further levels or special stains, or when older slides for the patient have been retrieved from the archive for comparison. The following fieldnote extract provides one consultant's description as she matches up newly arrived slides with the appropriate case, highlighting the manual and potentially time-consuming nature of this process:

'So this is my place for things waiting for extras to come. So now I'm going to match up. So that's [patient name] and that's [same patient name]. That looks like that one doesn't it, [patient name] [same patient name]? [patient name] [same patient name]. [...] And those are still waiting for more work to come. [...] [patient *name]. That's a compl*icated tumour one. So I need to try and finish that one off today. [patient name]. That was *the funny Durham one except I can't remember what I've done with them.* [...] *So it's like playing patience isn't* it, you end up with all the different piles on your desk, all *your cards and you're trying to pile them up next to each other.' (*CH3)

Most histopathologists have a number of document trays in their office for organising their cases:

On his desk, CH8 *has a number of trays for organising his work, including an 'in tray'. One labelled 'special stains' contains* cases where CH8 *is 'waiting for stuff', e.g. waiting for additional slides, waiting for slides from* the archive. Having sorted through his pile of cases, CH8 puts the non-urgent ones in the back of his in tray, while the high priority cases sit in a pile on his desk, so that he can start with those. The cases that he has finished with – he has authorised and finished the paperwork – sit in a tray on the floor. CH8 also has an additional tray on his desk for when things get busy.

Fig. 3: Document trays for organising cases

4.2 Gathering information

For each case, prior to looking at the slides, there is usually a process of gathering information. The histopathologist typically begins by looking at the clinical details for the patient. The slides come with a histopathology request form (sometimes called a requisition form), which will have been completed by the requesting clinician. A copy of the patient's consent form may also be received. If the case is a referral from outside the hospital Trust, a referral letter may also be attached. The request form provides the patient's name, age, relevant clinical history and what the requesting clinician considers to be possible diagnoses. In providing the possible diagnoses, the request form provides the questions that the report should answer, the diagnoses that the report should confirm or reject. In this way, the information on the request form provides a framework that guides the histopathologist's diagnosis:

*'I just look at the clinical details, so what are they after? So here they're talking about a cyst and they've sucked some fluid out but there's still a lump there. So they've taken a biopsy. So, in the biopsy I want to see if there's any cause to explain a lump. Specifically, I'm looking to see if there's a cyst.' (*CH4)

On the request form, information about the specimen is given: where the parts of the specimen were taken from and, where relevant, how the part was taken. This information will alert the histopathologist to the likelihood of the specimen containing the necessary diagnostic information:

'I also notice that it's a clinical [...] a lot of the cores that we take for the breast, things are done under image guidance so either x-*ray or ultrasound control so it's done on video and you can see that the needle is in the lesion. In this case he's fumbled around and we know that there's a high chance that they've* missed the thing *that caused the lump.' (*CH4)

If a colonoscopy or endoscopy has been carried out while undertaking the biopsy, the report of this, with images, may be provided. Again, this gives the histopathologist an indication of what to look for:

'They've given us the endoscopy report this time. [Pause while looking at the endoscopy report] He's on something called PPI which is a drug which makes it difficult to diagnose this helicobacter thing any other way *so that it's reasonable in that case to use histology to determine whether it's there or not. So we'll do that. So. They've just seen gastritis so they've just seen inflammation and they're not expecting there to be a cancer or an ulcer or anything here. So I've got that in the back of my mind when I'm looking at these.' (*CH3)

What also became apparent in the observations however was the occasional absence of information, as in the following fieldnote extract where it was unclear which part of the body the skin sample had been taken from:

'[The request form] doesn't say, I don't think it says leg at all. But I think that [on the consent form] says right leg. Pretty sure but I'll put [a] question mark. As I say, sometimes there's more clinical detail on the consent form than there is on the reque*st form.' (*CH2)

Additional information such as the endoscopy report was not always provided:

'Often we get a copy of the endoscopy report so we can see what they saw when they were looking [down the] colonoscope *but we haven't got that this time so we haven't got a good description of what they saw and suspect to correlate this with.' (*CH3)

Other times, there was ambiguity in the information on the request form:

*'So does that mean they've got two different lesions? Not very clear is it from that.' (*CH5)

A possible diagnosis was not always given on the request form, and in such situations the histopathologist appeared to draw on their knowledge of typical reasons for undertaking a particular investigation in order to determine what it was they were being asked to look for:

'We don't know, they haven't told us what the indications are for endoscopy so we don't know why they've biopsied the duodenum of this lady who is [pause while looking at the clinical details] quite senior. But most of the time they do duodenal biopsies because people have symptoms that might suggest celiac disease. [...] So I *assume that's what it is here.' (*CH3)

Often, the information on the request form and additional reports that came with it, such as the endoscopy report, was the only information that was referred to, although the histopathologist may also refer to the consent form to gather information, as in the example above. Some histopathologists begin dictating their report at this stage, reading the patient's name, hospital number and clinical details from the request form. The histopathologist may return to these paper-based sources of information once they have begun viewing the slides. In fact, in our observations, histopathologists frequently glanced back to the request form, for example, to check the description of the slide that they were currently looking at.

The histopathologist can also use the laboratory information system to access the description of the 'macro' (the macroscopic or gross description of the specimen) which the histopathologist would have dictated during cut-up:

'This is a specimen that I cut up the other day [...] And so because [...] *I did hundreds of them, so I can't* remember which one, so I just look up the macro. [...] *And so I just want to look it up just to make sure I didn't see anything odd.' (*CH9)

Looking at the description of the macro was an activity that we observed three of the histopathologists carrying out. Two of them did this regularly, one of whom brought up the macro for all of the cases and often looked back to it while viewing the slides. Previous histopathology reports for the patient can also be accessed from the laboratory information system. Checking for previous reports was an activity carried out regularly by two of the histopathologists that we observed.

An additional source of information that the histopathologist may draw on once they have begun viewing the slides is reference books. These can help the histopathologist to confirm a diagnosis or they may point to other diagnoses that the histopathologist should be considering:

'I'm just wondering, perineurioma, which is a pretty rare thing. So I get [my] extra large text book on soft tissue *lumps and bumps ['Soft Tissue Tumours'] which is pretty much up to date.* [...] [Looks up perineurioma in *index] It's not intraneural. [Reads out relevant section from the book] Right, well it could be perineurioma.'* (CH2)

4.3 Viewing the slides

Having read the information on the request form and any other relevant information, the histopathologist then begins to look at the slides. Before placing the first slide on the microscope, the histopathologist checks that there is the right number of slides and that the name and specimen number on the slides matches those on the request form. For certain slides, they may also annotate them before viewing them, in order to ease navigating the slide, for example, drawing lines between the different levels or circling the areas of the slide where the tissue is. The histopathologist typically views the slides in the order that they are placed in the tray.

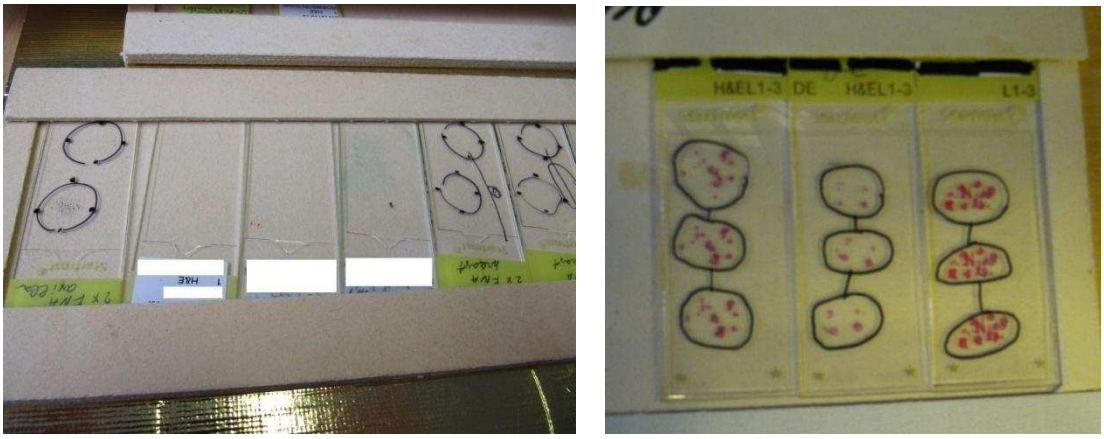

Fig. 5: Annotations to assist navigating slide

While most microscopes have lenses that range from 2.5x to 40x magnification, some of the histopathologists that we observed had additional lenses, such as a 1.6x lens for a particularly low power view and a 63x lens for a particularly high power view. The level of magnification used appears to vary according to the histopathologist, depending of their specialty, their level of experience and their personal preference. For example, one breast histopathologist we observed worked predominantly at 2.5x. However, we can identify a general pattern of an initial scan at low power, followed by zooming in on areas of interest. Having read the request form, the histopathologist will begin with one or more high level questions that they are seeking to answer, e.g. 'Does this person have cancer?' At low power, histopathologists are looking at the 'overall architecture':

*'Low power that alerts me to something being not right is if there's more cells and it looks expanded [...] it's like a little village and it's got the roads joining up, it's not a sprawling urban sprawl which is what a cancer is. So I look very quickly at that, look at the ratio of everything, I suppose I do, I don't know, I just look at it and know that it's normal or benign.' (*CH4)

New questions may arise when looking at the slide at low power, requiring the histopathologist to zoom in to look in more detail at particular areas. For example, consider the following extract, where having identified at low power that the patient has cancer, the histopathologist zooms in to determine the stage of the cancer and whether it is an in situ cancer:

'At the lowest power I can see straight away. So straightforward malignancy. At the very lowest power you can see it's just a mess. At higher power I can see... [zooms in] actually there's two things here. There's the tumour which are the bigger pinker cells and *there's also a lot of lymphocy*tes, the smaller dotty things, yeah? So *there's an invasive cancer and but also there is tumour like that, can you see it's a rounded configuration, that's an in situ cancer. So that's the earliest stage so we've got the early stage and the invasive cancer.' (*CH4)

The diagnosis may also require particular information, obtained at high power, for grading. For example, in breast cancer, the size and shape of the nuclei are used to establish a nucleus score and a mitotic count is achieved by counting the number of mitotic figures in ten high power fields.

While looking at the slides, the histopathologist adjusts their expectation of finding something of concern:

*'This is level three of the slide, and usually if they look normal and the clinicians are expecting this site to be normal and I look at one level very carefully and I don't see any abnormality then it's probably going to be okay.' (*CH3)

They also have to assess whether they have adequate evidence to support a particular diagnosis:

*'So I need to decide whether I've got enough evidence on the basis of this slide to write my report o*r whether, I can always ask for some extra levels down through the block and that would give me some more views of *whatever this thing is.' (*CH3)

For this reason, identifying certain features may initiate a hunt for further examples, as in the following fieldnote extract:

'It's a stain for a very tiny bacteria, TB bacteria [...] Now when I've seen one that's highly suspicious I have to look really hard and that's why I've gone on 40x. [...] I would prefer to see more of them than just one or two. And so I have to go back hunting for them now. [...] And my suspicion, my index of suspicion is extremely high. I think they are what they are. Because you can get things that look like that that are just debris and residue. Not very convincing but still. You do *really spend an awful lot of time looking for these. I'll look for them in specific* areas rather than anywhere. [...] [changes to slide 10, 40x] This is a more sensitive stain and I think it *highlights a bit better [?]. Ah, [?] two there. [...]I'm convince*d this is myco*bacteria 'cos I've started seeing more and more. You see one, you see two, I'm not sure of it, you start seeing a bit more. [...]But they're not teeming with it you see, that's why, sometimes there are zillions of it and then there is never a* problem. When *you have few...' (*CH10)

Similarly, where two features are identified together, this may initiate a hunt to determine if those two features are always located together within the tissue, as in the following example:

'I'm looking over at bits like that where they've got very small basal nuclei and mutinous cytoplasm, atypical cytoplasm, and then down the*re where there's a much higher NC [nuclear/cytoplasmic] ratio than, there's more pink, is that just because it's really acutely inflamed over there and it's a sort of chicken and egg thing there, you know, is there lots of acute inflammation there because these are more atypical glands, and so that's the body's response to the more atypical gland, it knows they're more atypical, or are they* like that because of the *inflammation here. So that's why again it's quite useful looking at this power to see how those two areas relate to each other and I'm looking round here, round the edge now, thinking there's just no inflammation round here* and tho*se glands don't look like that and then where they do look like that there's inflammation.' (*CH5)

The histopathologist may annotate areas of concern, either for their own reference, in order to get a second opinion from a colleague, or in order to be able to show the relevant part of the slide in the MDT meeting:

*'I'm going to put a dot next to them because this will be reviewed at the MDT meeting [marks area*s of concern *with a pen]. So that will save whoever's doing the review, it won't be me because I don't go to that meeting, so that person can find my dots and not have to spend a lot of time reviewing the case in its entirety.' (*CH3)

Fig. 6: Annotating areas of concern

Having viewed a slide, the histopathologist places it back in the tray. Some histopathologists turn the slide upside down so that, at a glance, they can see which slides they have already viewed.

4.3.1 Making comparisons between slides

In addition to the kinds of diagnostic search strategies described above, we also see histopathologists making comparisons between slides. An example of this is where the histopathologist has previously given a report on a frozen section and subsequently receives the H&E slides. They have to decide whether the diagnosis they made on the basis of the frozen section still stands, as in the following fieldnote extract:

*'So this is the frozen. [Puts slide on] [...] Looks pretty similar. Not as n*ice a section because this has not been *fixed and processed. This is sent fresh, cut and stained. Fresh tissue. I was just checking it didn't look completely different.' (*CH2)

Another comparison that we observed was where the histopathologist has received slides with skin samples from two different sites on the body. Looking at the second slide, the histopathologist was able to come to a diagnosis, so he then returned to the second slide to determine whether the diagnosis was the same for both sites:

'I'll just have a look at [part] A again. [...] *it's sort of similar but not... it's pretty non* specific. [...] Could be the *same, it probably is the same but it's not as good an example.' (*CH2)

These examples also highlight the way in which histopathologists do not simply look at the slides once, in order, but may need to return to particular slides, based on what they see on other slides. With each slide, the histopathologist is revising their hypothesis with regard to the diagnosis, which may require them to look at previous slides in light of their revised hypothesis:

There are 7 slides. CH8 starts with the first slide on the right. [...] He says that he thinks the patient has the disease that the consultant thinks that he has. The slide has three pieces of tissue on it. CH8 looks just at the first one and a half pieces of tissue. He says that he knows that the other slide (due to the special stain) will *diagnose completely so he looks at that next. 'Bizarrely, it doesn't show what I thought it would show.' [...] He* goes back to the first slide, looks at the third level of tissue.

Histopathologists may also request previous slides from the archive, in order to be able to compare with the most recent slides. Retrieving slides from the archive usually requires the histopathologist to complete a request form specifying the requisition number of the slide that is required. Looking at previous slides allows them to determine if the condition has got worse. Additionally, looking at the most recent slides may lead to the histopathologist questioning the previous diagnosis:

CH8 says that he would like to see the previous slides. There was inflammation last time but not this time, raising the question of whether there was really inflammation last time.

4.3.2 Requesting extra slides

Having viewed the slides, the histopathologist may decide that they need to either get some additional levels cut or to get some special stains, so they complete an 'extra work request' form. Getting extra levels cut means requesting the laboratory take the paraffin block and cut further sections from it, going deeper into the tissue within it. It tends to occur when nothing suspicious has been found, to make sure that they have not missed anything:

*'I probably should just do two levels just 'cos, to cut into it a little bit more, just to make sure it's all alright and there's nothing hiding. Because melanomas can aris*e in moles and we might have just been very unlucky and *missed the bad bit when we were chopping it up. I know I'll feel better if we just cut into it a little bit more, just to check it out.' (*CH2)

Special stains are ordered to confirm or refute a particular diagnosis and so depend on what the histopathologist currently considers to be possible diagnoses. In both cases, the histopathologist has to weigh up the cost of the delay caused by requesting the extra work and the benefit of the additional information that will be provided by the extra work:

*'There's a bacteria that causes inflammation sometimes which if you're very careful and you're very lucky you can just about see on this H&E stain. And if I can't see it, which I can't, and if it was impo*rtant to decide *whether it's really there or not then I would need to ask for another stain which obviously would either delay*

everything or lead to me issuing a supplementary report. [...] So I'm spending a bit of time because I'm seeing if I can avoiding *doing an extra circuit of work for this one. But I don't think I can.' (*CH3)

Where the histopathologist has multiple slides, they have to choose which slide to use for the extra levels and special stains. For example, for special stains, they may compare the slides to decide which has the most tumour in it:

*'Which has got the most tumour in it? Both got good amount in. That's got that, that and that. That's got that and that. Suppose number one's got slightly more but doesn't really matter. Going to ch*oose one for my immuno *panel.' (*CH2)

Some histopathologists have a notebook where they record any requests that they make for extra work or for slides from archive, as there is a risk that you may make a request, not receive the slides, and forget that they were requested, so that the case remained unreported. On one occasion, a histopathologist was observed to receive further levels following an extra work request but the levels had been taken from the wrong sample. However, the histopathologist still needed to check these slides to ensure there was no additional diagnostic information contained within them.

4.3.3 Getting a second opinion

While existing studies of histpathology focus on the histopathologist working alone at their microscope, we observed much collaboration between histopathologists, with histopathologists regularly seeking second opinions from their colleagues. Getting second opinions within the department is quite informal. The histopathologist may decide to get a second opinion straight away and so take the slides down the corridor to a colleague, something that we observed twice during our observations. Most histopathologists have a double headed microscope so they may look at the slides together, although this is not always a straightforward task, as the fieldnote extract below indicates:

A colleague comes in to CH*5's office so* CH5 asks him if he would mind looking at this case. They look at the slides together on the microscope. [...]
Colleague: What about the edge, eleven o'clock where...
CH*5: Sorry, if the arrow's pointing north...*
Colleague: South east. [CH*5 navigates] That's south west.*
CH*5: Oh yeah, that's south west.* [...]
Colleague: Further on, further on, keep going, keep going, keep going, keep going. To the bit where there *wasn't the [?] stuff, there, this stuff. That's not normal, is it?*

Alternatively, the histopathologist may wait and give their colleague the case to look at on their own:

CH8 receives slides back from [consultant name], following a second opinion. [...] There is a post-it note attached to the tray. CH8 had written on the post-it note the patient number and what he thought was the

diagnosis. He'd dotted on the slide what he thinks it's important to look at, although he doesn't know which slides [consultant name] has actually looked at. [Consultant name] has written on the post-it note, saying what he thinks the diagnosis is. CH8 opens the report for this case on his computer, which he has not yet authorised. He had previously written his diagnosis and what he thought [consultant name] would say. On the report he states that the slides have been seen by another consultant who agrees with his diagnosis.

Histopathologists also seek second opinions from colleagues elsewhere, both within the UK and internationally.

If a histopathologist is faced with a complex case, they may also leave a case and come back to it:

'I've been reporting since nine o'clock and that's quite intensive for looking down a microscope and because this is quite difficult [...] Colleagues of mine used to call it the bench test. You leave it on the bench over night *and see if it gets easier. It isn't difficult, it's just out of the ordinary and that's exactly what I'm going to do.'* (CH9)

4.4 Reporting a case

Having viewed some or all of the slides, the histopathologist can then begin the process of producing a report. When to begin dictating the report depends on both the nature of the case and the histopathologist's preference:

'The other thing I have to decide is whether I want to write a report [now]. *This case is complicated because it's* got six different [parts]. Do I want to write one report that encompasses all six bits or do I want to group them? And also do I want to keep it all in my head until I get to the end and then do it all in one go or do I want to *divide it up as I go along? Um, and because the ones I've looked at so far don't have anything the matter with* them I can manage to keep that in my head [...] [Takes slide off and puts slide 4 on] But [part] E, sigmoid lesion, this slide has just [part] *E on it, [checking the request form]. And that's* [part] F. Right, so this is lots of bits from part E then. So this is where they think *there's something the matter and they're right, there is. So we've got abnormality here which means that the easiest way to structure the report will be to deal with everything we've got to up 'til now and then start a new line for this one. So that's what I'll do.' (*CH3)

In fact, the activities of viewing the slide and reporting are very much interleaved, and often the histopathologist will continue viewing the slide while dictating their report:

*'So I've had a look at all four of the levels now and then I'll choose my favourite one to concentrate on and do the whole report, now that I've reassured myself that there's nothing in some levels that aren't in others.' (*CH3)

While most histopathologists dictate their reports, some write their reports on the back of the request form and one histopathologist that we observed used voice recognition for some of her reports. Some of the histopathologists have quick text codes for certain diagnoses, which they just write on the front of the request form and which the secretaries then use to generate a report. Even if dictating their report, the histopathologist will still write a summary of the diagnosis and the date on the front of the request form. They do this so that

when it comes to authorising the report they can check that the correct diagnosis has been entered into the report. If there is a subsequent delay in producing the report, they also have a record of when they reported the case.

If the histopathologist has submitted an extra work request or has requested slides from the archive, they may dictate a report based on what they have seen and then later edit this based on what is seen in the additional slides or they may later issue a 'supplementary report'. Alternatively, they may wait until the extra work is received before reporting the case. Whichever they do, when they receive the extra work, they are likely to look at the original slides again. If they have dictated a report, they may view that report. One histopathologist that we observed routinely takes photographs down her microscope of important features and then uses these to report from, but she was also able to use these photographs when returning to a case, to save her looking through all the slides again:

*'So these are the pictures I took yesterday [looks at photographs of slide on computer] and I'm just reminding myself of them, reminding what I'm interested in etcetera etcetera.' (*CH9)

In fact, histopathologists will often return to a case, not only because they have requested extra work or have requested slides from the archive, but also on receiving the second opinion of a colleague, on receiving paraffin slides having initially given a diagnosis on a frozen section, in preparing for a MDT meeting (sometimes reviewing cases with colleagues on a multiheaded microscope), on having gathered more information about the patient in the MDT meeting, or simply because it is a complex case and so they have given themselves time to think it over as described above.

If dictating a report, the audio files have to then be uploaded to the computer system so that they can be accessed by the secretarial staff. The request forms are then passed to the secretarial staff, who find the appropriate dictation file and type the report. Once this is done, the request form is passed back to the histopathologist, who has to use the lab system to open the report and authorise it. At this stage they check that the diagnosis in the report matches the diagnosis that they have written on the front of the request form and correct any transcription errors. They then authorise the report.

Once a report has been authorised, it is sent to the clinician who submitted the histopathology request form, who may be based in the same hospital or at a different site or Trust. A paper report is printed in a daily batched print run, and secretaries collate all of the reports for each individual clinician before posting them. In addition, an electronic report is sent to the Trust's results service system where it can be viewed on the Trust intranet. However, the histopathologist has no way of knowing whether their reports have been received and read:

CH8 *completes a 'Supplementary report', having previously submitted the main/prima*ry report. This is to go to another centre. CH8 wants to make sure that the doctor receives it. CH8 has no contact details for the doctor looking after the patient, so he emails his secretary to get a phone number for the doctor. He puts a post-it note on *the top of the tray, writing 'Call* [centre name]*'.*

4.5 The histopathologist's office

A noticeable feature of the histopathologists' offices was the different physical layouts in terms of where the computer was placed in relation to the microscope. Those who regularly used the laboratory information system had the microscope and the computer next to each other, so that they were able to refer to information on the computer while working at the microscope. In contrast, others had their microscope on a different desk to the computer, separating these two aspects of their work.

Fig. 4: Different layouts

More generally, we can observe the way in which histopathologists' personalise their office space and their microscope in order to create a pleasant working environment. The histopathologists we observed had personalised their offices by hanging pictures on the walls, putting up photographs of family or drawings by their children, and bringing in plants, and a couple of those that we observed regularly listen to music while they work. A complaint of some of the histopathologists related to the 'piles of glass' in their offices and the removal of these is one way in which the introduction of a digital microscope could improve the working environment.

5. Discussion

Having described the process of coming to a diagnosis at and around the microscope, we are able to highlight a number of 'ultra-practical' issues (Schmidt et al. 2007) to be considered in designing a digital microscope. However, it is important not to be restricted in our thinking by what the conventional microscope allows; the move to digital allows us to move beyond real world constraints (Dodds and Ruddle 2009) to what are sometimes referred to as 'magic' interfaces (Bowman et al. 2004). By looking at the whole process of building up a diagnosis, not just looking at how the slides are navigated, our study highlights a number of ways in which a digital microscope could go further than simply allowing the viewing of slides. These are presented below, organised around the following themes: supporting a day's work (Section 5.1), building up a diagnosis (Section 5.2), information requirements (Section 5.3), and aesthetic requirements (Section 5.4). We conclude by considering the generalisability of our findings and recommendations.

5.1 Supporting a day's work

An important benefit that could be provided by a digital microscope is removal of the time spent by histopathologists organising cases. As others have noted, rather than waiting for previous slides to be retrieved from the archive and then matching them up with the appropriate case, histopathologists could access previous

slides when they are needed (Cross et al. 2002). When special stains 'arrive', these could automatically be added to the appropriate case and the status of the case updated in the histopathologist's list of cases to indicate that the necessary slides are now available. The histopathologist's list of cases could automatically be organised according to urgency. However, the organising of cases needs to allow flexibility, so that histopathologists are able to organise cases not just according to urgency but also considering their preferred way of working.

What also requires consideration is how to present information at the case list level. With the current system of glass slides in trays, much information is available at a glance – a rough estimate of the number of cases; the number of those that are urgent, indicated by red stickers; and a rough estimate of the size of individual cases. With a digital microscope, this information must remain as easily accessible.

5.2 Building up a diagnosis

An overall theme in the data is the way in which a diagnosis is 'built up'. The histopathologist starts with a complete case, with a number of slides and the clinical details, but through the process of diagnosis, it is certain elements of the slides that become important in determining and justifying the diagnosis. First of all, certain elements of the request form are drawn out and used to develop a hypothesis. The histopathologist views the slides, identifying particular features, and these features are used to either confirm or revise the hypothesis. As the hypothesis is revised, it may be necessary to return to earlier slides in light of the new hypothesis. Particular features become important, as the basis for the diagnosis. The histopathologist may annotate these features, and these features become the basis for the subsequent report. While certainly not a common practice, the habit of one of the histopathologists of photographing relevant parts of relevant slides nicely illustrates this idea of identifying and pulling together relevant features. We also see histopathologists comparing features across slides.

Also noticeable in the data is how often a case is returned to, that it is not simply a case of looking at the slides once and dictating a report, again something that is absent from existing studies of histopathology.

These findings suggest two important requirements for a digital microscope. Firstly, it should allow multiple slides to be shown at the same time, supporting the histopathologist in making comparisons across slides. Secondly, a digital microscope should allow the 'extraction' or 'capture' of relevant parts of a slide, whether for comparison within or across slides, to support the creation of the report, or to return to later. Useful tools would be the ability to take a snapshot of a particular area of the slide and a browsing history that allows the histopathologist to see which parts of a case they have already viewed.

5.3 Information requirements

The findings highlight the need to integrate other tasks and information with the viewing of the slide. While discussion of digital microscopy often focuses on the histopathologist's interpretation of the slide, we see that this interpretation takes place in the context of a range of pieces of information about the patient. Diagnostic work does not begin and end at the microscope but incorporates other activities such as comparing what is seen on the slide with images in reference books, producing a report, and discussing cases with colleagues.

5.4 Aesthetic requirements

A final issue concerns the impact that introducing a digital microscope would have on the working environment. There is growing acknowledgement within HCI of the need to consider 'the individual, social, cultural and physical aspects of human experience of space and place' when designing new technologies, on the basis that the introduction of new technologies impacts our experience of the places they inhabit while, at the same time, the way in which we perceive a technology is impacted by the physical environment (Ciolfi 2004). However, such arguments for understanding the use of space and place tend to focus on the design of ubiquitous and mobile technologies. Similarly, there is growing acknowledgement of the need to consider aesthetics in the design of new technologies. There has been discussion of aesthetics in the literature when introducing healthcare technologies into patients' homes (Axelrod et al. 2009). However, with the exception of Rullo's (2008) work on technology design for a neonatal intensive care unit, this is not an issue that has been explored in relation to healthcare technologies to be used in a hospital environment.

We have described how different histopathologists set up their offices in different ways, reflecting their preferred way of working. However, as noted above, important information can be obtained at a glance with such piles and it is for this reason that, in other working environments, it has been found that 'piling' remains as the dominant form of information management (Buttfield-Addison et al. 2009).

At the same time, the introduction of a digital microscope would likely be accompanied by requirements in relation to lighting levels, as has been the case in radiology, in order to prevent reflection and glare and to reduce fatigue, both of which have the potential to negatively impact efficiency and accuracy (Goyal et al. 2009). Although such requirements are important, the need to sit in a darkened room may act as a real barrier to the introduction of digital pathology. While there is no obvious answer to this dilemma, it reminds us of the need to consider not only the design of the technology but the design of the broader environment.

5.5 Limitations and future work

The findings presented in this paper are based on a study of one histopathology department in a UK hospital. As such we cannot make any claims about the generalisability of our findings or the extent to which our recommendations are immediately applicable to other histopathology departments. In future work, we hope to study other histopathology departments. This would be an important step towards establishing a conceptual model of diagnostic work in histopathology that is based on the details of work practice, thereby providing a framework that can be used to support the design of a digital microscope.

The way in which the microscope enables the histopathologists to easily move between viewing the slide and glancing at the request form raises the question of what information should be displayed on a digital microscope and the layout and nature of the display. While the obvious solution is to provide all information relating to a case via the display, this may negatively impact the histopathologist's ability to be completely focused on the slide. An alternative is to have multiple displays, one for viewing slides and one for accessing other information relating to the case, as is currently done in radiology. The potential and impact of different set ups should be

explored experimentally. There is also the issue that different histopathologists like to work in different ways, some separating their work at the microscope from their work at the computer, raising the question of whether such a variety of approaches could be supported.

Acknowledgements

We are very grateful to all the histopathologists at Leeds Teaching Hospitals NHS Trust who enabled us to undertake this work by allowing us to observe them. We would like to thank Professor Phil Quirke for his feedback on this paper. This report is independent research commissioned by the National Institute for Health Research. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. The authors acknowledge the support of the National Institute for Health Research, through the Comprehensive Clinical Research Network.

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