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REVIEW ARTICLE

Virtual microscopy and digital pathology in training and education

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Traditionally, education and training in pathology has been delivered using textbooks, glass slides and conventional microscopy. Over the last two decades, the number of web-based pathology resources has expanded dramatically with centralized pathological resources being delivered to many students simultaneously. Recently, whole slide imaging technology allows glass slides to be scanned and viewed on a computer screen via dedicated software. This technology is referred to as virtual microscopy and has created enormous opportunities in pathological training and education. Students are able to learn key histopathological skills, e.g. to identify areas of diagnostic relevance from an entire slide, via a web-based computer environment. Students no longer need to be in the same room as the slides. New human–computer interfaces are also being developed using more natural touch technology to enhance the manipulation of digitized slides. Several major initiatives are also underway introducing online competency and diagnostic decision analysis using virtual microscopy and have important future roles in accreditation and recertification. Finally, researchers are investigating how pathological decision-making is achieved using virtual microscopy and modern eye-tracking devices. Virtual microscopy and digital pathology will continue to improve how pathology training and education is delivered.

Key words: Digital pathology; education; review; training; virtual microscopy.

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Education and training in histology, anatomical pathology and cytopathology remain essential to both undergraduate and postgraduate courses in pathology and for residency training in pathology. Previously, this would have been delivered using textbooks, glass slides and conventional microscopy, but increasingly web-based resources have been developed to supplement or replace the more traditional methodologies. Web-resources in pathology have expanded dramatically in the last 20 years. Although the quality has often been variable, there have been clear benefits in centralizing resources that can be delivered to many students simultaneously. This has greatly aided departments, colleges and professional organisations in delivering histology training to a wider audience in a more cost-effective way.

Recently, however, an additional tool, 'Whole Slide Imaging' has revolutionized the way in which histology and histopathology can be delivered on-line by providing the ability to scan entire glass slides at diagnostic resolution. This creates a digital slide of the tissue section, which, using software can be viewed on a computer screen. The slide can be tracked in the x and y axes and magnified in

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real time, very much like using a standard microscope. This is often referred to as virtual microscopy, as it happens digitally. These images can be extremely large: circa 300 k by 100 k pixels and several gigabytes in size. As such, they are too big to be loaded into computer memory at once or to be downloaded across the Internet in their entirety. Rather, the nature of the image is defined such that regions of the image can be requested and displayed in turn, removing the need to load the entire image. As the user moves across the image, the relevant areas of the image are rapidly loaded to the screen. This allows virtual microscopy to be delivered across the web via standard browser technology, giving users access to entire digital slides rather than small restricted photomicrographs of predefined regions of interest.

This has enormous educational advantages. One of the key skills that histopathologists need to learn is the ability to identify areas of diagnostic relevance from an entire sample. Virtual microscopy allows this skill to be developed in a web-based environment where the student/trainee can see the morphologic patterns or diagnostic feature in the context of the entire sample. Training on tissue sections is not restricted to being in the same room as the glass slide, but can now be provided remotely and virtually from whole slide scans.

DIGITAL SLIDES FOR WEB-BASED EDUCATION

Appropriate software allows digital slides to be hosted on a centralized computer server and accessed by users anywhere in the world. The viewing software generally operates through a standard browser and allows the user to navigate the slide using on-screen controls. The user can 'drag and drop' the image on-screen to move around the slide or can move the image in discrete steps, left, right, up or down. An appropriate magnification can be selected from a discrete range or continuously changed by scrolling the mouse wheel to zoom in or out. The viewing software also provides a thumbnail overview of the entire slide, allowing users to maintain orientation and context, regardless of their magnification and position (Fig. 1). The thumbnail ensures that inexperienced users do not get 'lost' within the specimen, a common occurrence with conventional microscopes.

Another key benefit of virtual slides is that they can be digitally annotated. Here, particular features or areas of diagnostic relevance on the slide can be labelled and stored. These allow students to move quickly to itemized regions of the slide by selecting from a drop down list (Fig. 1). The marked area can also be made to reveal a legend containing more detailed information. While using the annotation function, users retain the ability to explore the slide in the normal way.

UNDERGRADUATE HISTOLOGY AND PATHOLOGY

To facilitate the teaching of microscopic anatomy and histopathology using virtual microscopy, many undergraduate medical schools are now replacing their old microscope labs with new computer labs (Fig. 2). For many institutions, this represents a more economical way of delivering histology teaching to ever increasing numbers of students. The cost of maintaining and occasionally replacing expensive microscopes together with creating and storing a glass slide collection tends to outweigh the cost of computer hardware and software. The institution also no longer needs to tie up exclusive lab space and technical staff, providing further potential for savings. From an educational stance, the use of virtual slides also ensures that all students see the same slide; that slide is the best and most representative in the collection, rather than one of inferior quality, and that poor microscope technique does not interfere with the learning experience. It also allows rare slides to be used without fear of breakage. Displaying the slide on a computer screen means that students can more easily discuss the content with each other, allowing for the use of group-work based approaches to teaching. This pedagogy was more difficult to pursue when students assessed a glass slide on their individual microscopes. For similar reasons, tutors have reported the greater ease with which they can now demonstrate aspects of the specimen in comparison

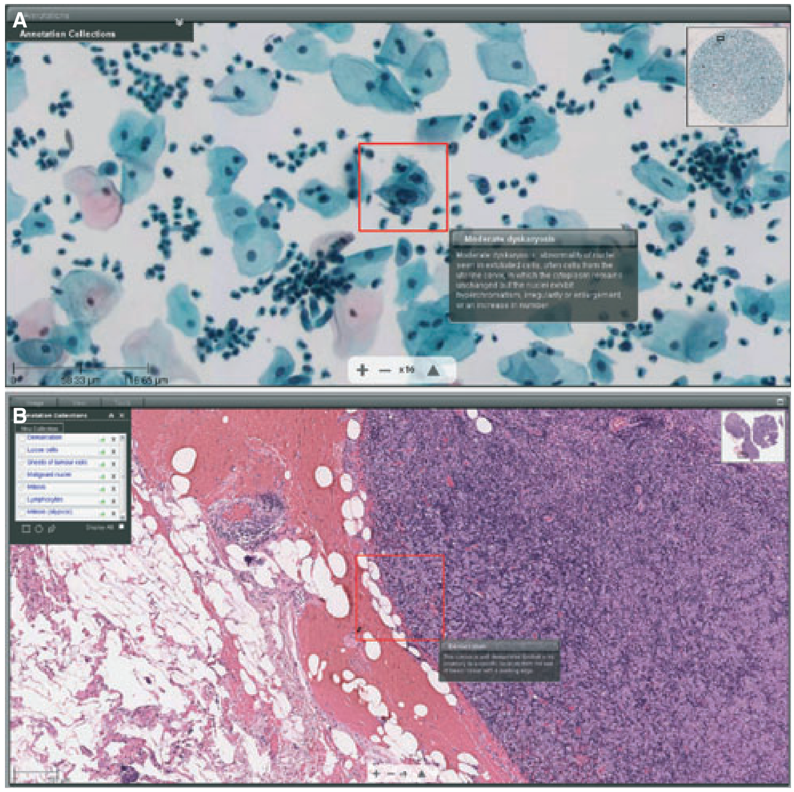

Fig. 1. An example of annotations in PathXL, showing how key features can be digitally marked and labelled on the slides. By clicking on an annotation label from the list (top left hand corner), the software relocates to that region of the slide, showing the important region of interest. Note also the thumbnail overview of the slide in the top right hand corner of the screen.

to conventional microscopy. Virtual microscopy has been shown to improve individual and group learning and enhance the overall learning experience (1–4). The fact that these tissue sections are digital also allows them to be incorporated into web-based self assessment tests or end-of-year examinations. A criticism levelled at virtual microscopy has been that it prevents students from the learning the skills of operating a microscope. This may be true, but in most centres, this is a separate objective to that of analysis and interpretation of tissue sections where the advantages of virtual microscopy clearly outweigh the disadvantages. Indeed, for many groups of students, the ability to operate a microscope successfully is completely irrelevant to their course.

Virtual microscopy also has the benefit of delivering histology courses to students outside the classroom setting. On-line virtual microscopy courses can be accessed by students anytime, anyplace allowing them to view slides that would have traditionally been restricted to the slide box and the classroom. The student no longer needs to be in the same room as the glass slide!

The replacement of a conventional histology laboratory with one capable of delivering a virtual microscopic anatomy course can be exemplified by the experience of Queen's University Belfast. In 2006, virtual slides were introduced to encourage greater engagement of microscopic anatomy by students. Although histology was an important foundation of key areas such as physiology, gross anatomy and pathology, many students perceived it as dull, and it had been difficult to motivate them sufficiently to participate actively in practical classes. To facilitate the adoption of virtual microscopy, the university invested in computers for the practical laboratory (Fig. 2) and a dedicated image server that used the Path-

Fig. 2. Photographs of the teaching laboratory showing students studying virtual slides.

XL^{TM} software platform to manage the digital slides and associated content into on-line subject-based modules (Fig. 3). The inclusion of electron micrographs, photographs or X-rays, which could be accessed alongside the virtual slide files, allowed modules to be specifically tailored to the needs of students on different degree pathways (e.g. medicine, dentistry, biomedical science and nursing).

In Queen's University Belfast, when virtual slides were first introduced into classes, the opinions of second year medical students were surveyed. These students had had a year studying histology using conventional microscopes, and of 136 who took part, 88% said they would prefer to use virtual microscopy. Eleven per cent claimed that implementing virtual slides would lead to a loss of microscopy skills, which they believed to be important. Nearly all students (99%) found the virtual slides easy to navigate, and 93% thought that virtual image quality was at least as good as that of a normal microscope. Tutors reported that students showed more interest in the slides. Similarly, in general, positive attitudes to the use of virtual slides have been reported before (1–4).

An examination requiring the analysis of the same previously unseen slide was set in two subsequent first year medical student cohorts. The first of these cohorts was taught using conventional slides, and the second was taught using virtual slides. There was a significant increase in performance from an average mark of 57% (n = 304) with conventional microscopy to 67% (n = 307) when virtual slides were used. This supports a study by Krippendorf and Lough (3) which demonstrated a significant improvement in exam performance by students who learnt using virtual microscopy when compared with those who used conventional microscopy. However, another study reported no differences in students' examination performance when comparing virtual and conventional microscopy as both learning and assessment tools (5). In the current study, the relatively large difference between cohorts may be explained by the fact

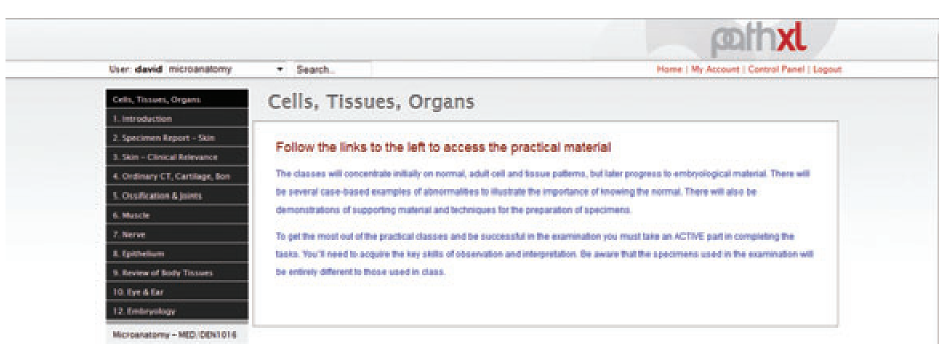

Fig. 3. Screenshot of the introductory page for the first year histology course for Queen's University medical students. Users can select the appropriate practical class from the list on the left. This will then lead them to the relevant virtual slides and support material. *Courtesy of Queen's University Belfast.

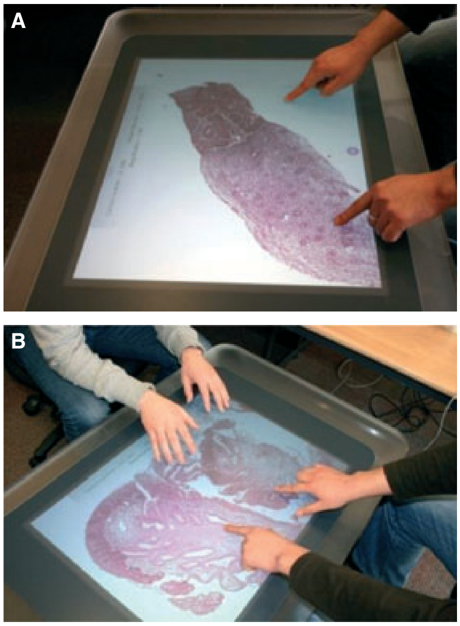

Fig. 4. Illustration of the microsoft surface virtual slide systems developed by Queen's University Belfast (6). This allows individual and groups to interact with the virtual slide using the touch sensitive screen.

Fig. 5. Virtual slides can now be viewed using iPad and other tablet devices. PathXL and Leica provide dedicated viewers for virtual microscopy. These will represent important technologies to make histology and histopathology learning more accessible to students.

that students have a short time to complete the test. In such circumstances, the observational analysis of a virtual slide can be accomplished more quickly than a glass slide on a microscope, allowing the examinee more time to write their report.

NEW INTERFACES FOR VIRTUAL MICROSCOPY AND EDUCATION

The increased use of virtual microscopy for education is driving research to explore new interfaces to manipulate and navigate slides. This closely follows other developments in consumer-based products and their human–computer user interfaces.

A key example of this is multitouch technology which allows individuals to interact with the computer screen, and objects on the screen, by multiple finger touch movements, removing the need for the keyboard or mouse. The authors have developed a multitouch table from Microsoft for the viewing of virtual slides (6,7) (Fig. 4). 'Squeezing' with the figures over the image reduces the magnification, expanding the figures outwards increases the magnification. Similarly swiping the figure over the image moves the image in a certain direction. These allow digital slides to be accessed via the web and manipulated using finger touch only. The surface table provides the ability for multiple users to interact simultaneously with a digital slide, again improving group learning in a friendly interactive environment.

Touch technology like this is typified by the development of touch screens within handheld smartphones and pad devices. This approach brings enormous benefits to virtual microscopy. A number of companies including Leica and PathXL currently provide iPad/iPhone viewers for virtual microscopy (Fig. 5). This type of interaction is very natural, and allows remote viewing of slides in a convenient handheld device.

The Institute for Molecular Medicine Finland has also developed a multitouch large 46-inch screen for digital slide interaction (8). This provides a larger interface to the digital slide. It is likely that there will be an expansion of new multitouch viewing technologies over the next few years.

One other advance of importance is the development of very large multi-screen viewers for virtual slides (9,10). An example of this is the Leeds Powerwall programme which has developed a large multi-screen panel of 28 high resolution monitors controlled by an 8-node cluster. The resulting image is 3.5 by 1.5 m in size, but has the same resolution as a conventional computer screen. This type of capability allows for high resolution pathology learning in a small group or classroom setting.

TRAINING IN PATHOLOGY

In the same way as virtual microscopy is supporting the delivery of undergraduate courses, it is also revolutionizing the web-based resources available for trainee or residents in diagnostic histopathology and cytopathology. The advantages here are the same as described previously: key is the ability to access the entire slide and understand pathological context as part of the diagnostic process.

Several major initiatives driven by individual institutions or professional organizations have seen the introduction of on-line training courses based on virtual microscopy. These are obviously aimed at supplementing rather than replacing conventional training practices, but represent a fabulous worldwide resource to both inexperienced and experienced pathologists. Many hundreds of slides, across different diseases and systems can be made available on-line for access and review at anytime and almost in anyplace. The ability to capture valuable slide sets collected over many years by well-respected teachers of pathology is of enormous benefit. Three examples serve to illustrate this. The first is the Rosai collection from Dr Jaun Rosai (www.rosaicollection.org) and sponsored by USCAP: a collection of nearly 20 000 surgical cases includes clinical history summaries, discussions and diagnoses. A similar series of slides collected by Dr Debbie Hopster over many years, and fully annotated with clinical and pathological background, are available from the Pathological Society of Great Britain and Ireland for training purposes (www.pathsoc.org). Finally, Leeds University in the UK have a very large series of digital slides across different diseases available to the general public (www.virtualpathology.leeds.ac.uk). This is only a small sample of what is now available online. As these types of resources grow, trainees of tomorrow will have, at the click of a mouse (or flick of the finger!), access to rich educational slide sets that they have never had before.

The use of virtual microscopy is also now playing a significant role in assessment, skill evaluation and competency. For example, the European Association of Pathology Chairs and Residency Program Directors (EAPCP) have undertaken a major project to harmonize training in Europe using an online competency test for residents in diagnostic pathology (11,12). This represents a mixture of question types, but importantly incorporates questions based on virtual slides (Fig. 6) that have been delivered to over 600 trainee pathologists at various stages of their training across 27 countries. This has allowed them to view virtual slides online, answer multiple choice questions and compare their performance with peers in the same stage of training, and in the same and different countries. These types of important initiatives are pushing the boundaries of what can be achieved in pathology training and assessment, and are helping to define standards of training from one country to another and even within the same training programme.

RECERTIFICATION

Developing new and reliable approaches to skill acquisition and testing diagnostic ability will present significant issues over the next few years. In 2005, the American Board of Medical Specialties approved an American Board of Pathology led Maintenance of Certification programme in pathology – requiring pathologists to undergo recertification procedure every 10 years (13). Part of this programme is labelled ‘cognitive expertise and evaluation of performance in practice’, and demands that pathologists are regularly tested to be ‘fit for practice’. Similar recertification requirements are being discussed in other parts of the world as a means of maintaining high-quality pathology practice. The effort required to revalidate the diagnostic skills of a very large number of pathologists is challenging and costly. Some

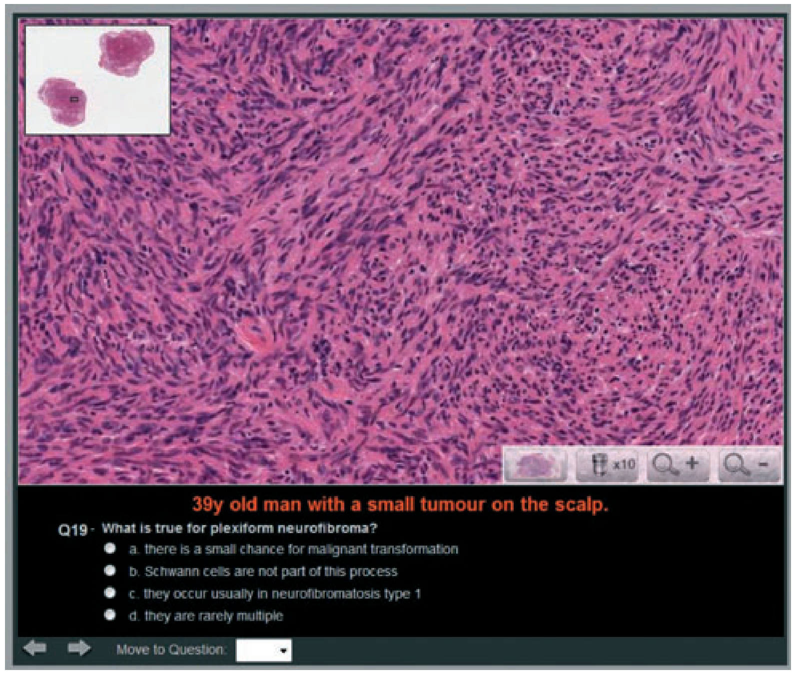

Fig. 6. Shows a typical question from the EAPCP examination.

have recognized that computer-based examinations and virtual microscopy represent a potential way forward (14).

NOVEL APPROACHES TO TRAINING AND EDUCATION

What makes a good diagnostic pathologist and how is this objectively measured? This is obviously important in defining aptitude tests, determining suitability for training investment, measuring diagnostic skill acquisition and fitness to practice. In training, to provide the trainee with objective (and proximate) feedback requires the trainer to be able to assess performance transparently through the use of metrics. This needs to be more than a multiple choice question-driven assessment of theoretical knowledge, and other approaches such as work-placed assessment and review of training log-books, are still highly subjective. This has been reviewed by Cross (15), but little research has been done to select appropriate tests and determine their reliability. To assess specific skills and apply objective metrics, a task needs to be broken into its essential components (task deconstruction), and then in each, determining what differentiates optimal from sub-optimal performance (16). This relies strongly on a deep understanding of visual interpretation and diagnostic decision by objectively deciphering the diagnostic process at a granular level.

The ability to manipulate digital slides and embed them in more complex learning environments presents enormous opportunities in developing virtual training environments in pathology and simulating diagnostic procedures. For example, we have developed a novel approach to learning using a combination of virtual slides, Bayesian Belief Networks and fuzzy logic language interpretation. The initial step in designing such a system is to get an experienced pathologist to deconstruct a diagnostic task into a distinct number of steps, each step involving the interpretation of a morphological/cellular clue. The final diagnosis is determined by the stepwise review of all of the clues. A diagnostic task represented in this way can be captured in the form of a Bayesian Belief Network that defines each of the steps and their relationship to the diagnosis (Fig. 7). By entering information on the characteristics

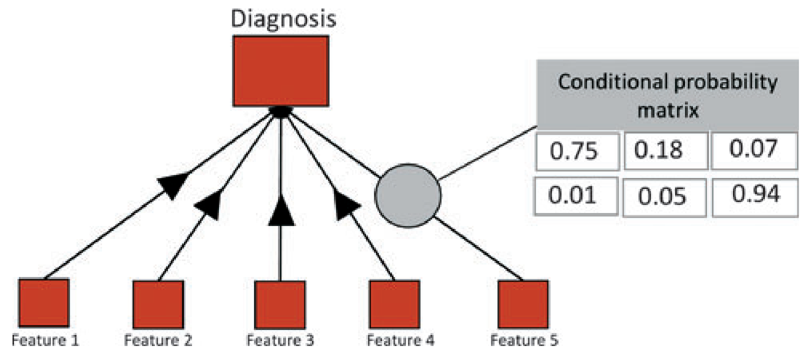

Fig. 7. Bayesian Belief Network design where morphological features (bottom nodes) represent evidence which when entered, update the diagnostic probability (top node). The impact that each feature has on the diagnosis is determined by the conditional probability matrix. Both the structure of the network and the weighting are defined by an experienced pathologist.

of the morphological clue, the belief network can use Bayes' theorem to update the probability of the diagnostic outcome. This provides a very strong model to structure and measure diagnostic decisions. The process of stepping through the diagnostic sequence allows a probability graph to be drawn, which effectively maps the diagnostic decision (Fig. 8). By recording a diagnostic decision made by an experienced pathologist, we have a standard that can be used to compare performance. Trainees can then view the same case and directly compare their interpretative performance relative to the expert in objective measureable terms (Fig. 9) (17–20). These approaches potentially allow different weights to be applied to each step in the diagnostic sequence – thereby allowing metering of the features and adjustment for bias, so that the overall decision is more controlled and reliable (18,19). They may therefore provide the basis to control cognitive bias – such as that demonstrated in the paper by Fandel (21). This has been built into a virtual learning environment that uses virtual slide sets and allows diagnostic simulation and training to be implemented in a consequence free environment. This not only provides a strong model for training and skill acquisition but also allows better

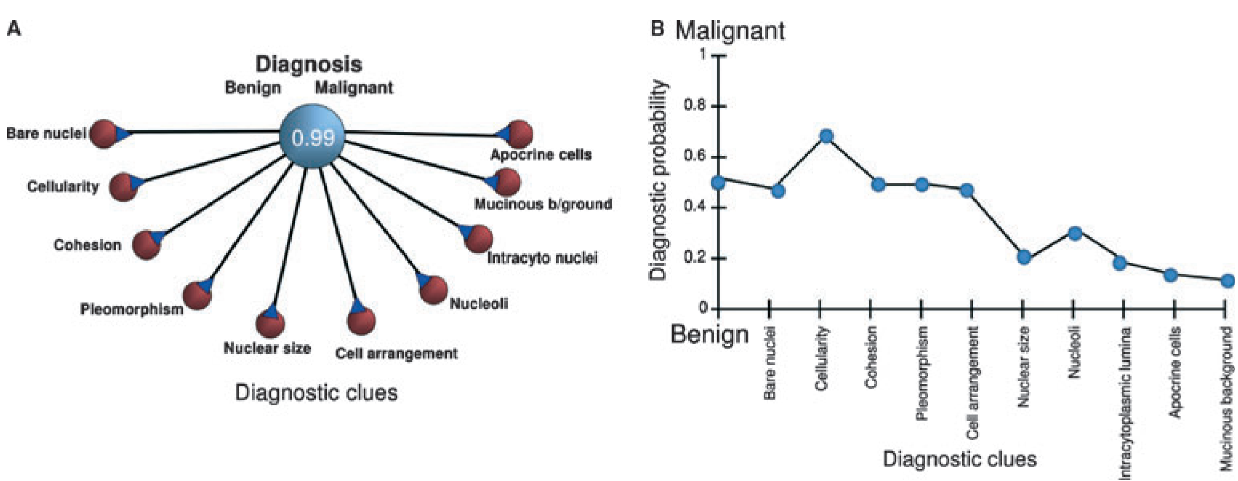

Fig. 8. Shows an example of a Bayesian Belief Network constructed for diagnosis in breast cytopathology20. As each clue is entered (Figure A), the diagnostic probability can be plotted (Figure B). This generates a unique and quantitative map of the decision sequence and the changing diagnostic probability. This quantitative map serves as a record of an experienced interpretation of a slide, and a standard against which others can be compared.

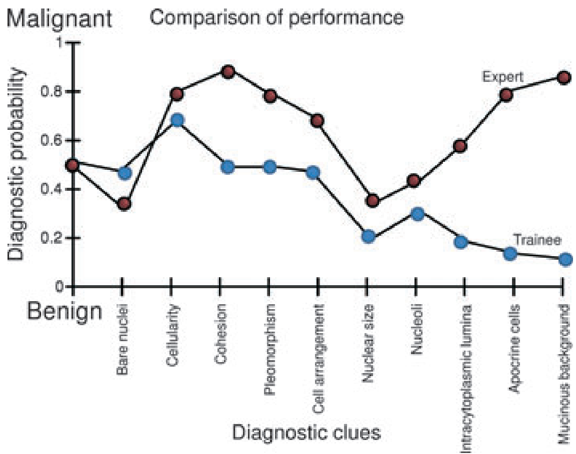

Fig. 9. Shows the comparison of a trainee decision map on a case vs an experts map for the same case. This allows trainees not only to evaluate the accuracy of their final decision but also the steps leading up to that decision. This gives trainees a unique insight into decision-making in pathology.

Fig. 10. Tracking of digital slides allows an analysis of search styles and their importance in diagnostic decision-making. They represent important training tools, allowing trainees to analyse their search patterns, slide coverage and compare this with expert pathologists.

approaches to determine competency in diagnostic pathology. This system is now available from PathXL (www.pathxl.com). The process is very rewarding for trainees/residents, in that it provides them with a sound logical sequence to follow, underpinning good diagnostic practice, even if after time, this process becomes subconscious. Errors in the decision-making process can be identified early and trapped. The most valuable metrics that pathology or any of the other medical specialties can provide are on errors. The whole point of training is to reduce errors, improve performance and make performance consistent (16). By objectively defining the diagnostic process using metric and simulation, errors are more easily identified.

USING VIRTUAL MICROSCOPY TO UNDERSTAND DECISION-MAKING BY PATHOLOGISTS

How pathologists make decisions and how such decision-making skills can be measured and communicated to students is poorly understood (22). One interesting aspect of this is studying how eye movement across a specimen relates to search skills when studying tissue section patterns. Virtual microscopy provides the ideal tool for exploring in detail how slide navigation contributes to diagnostic interpretation (Fig. 10). Movement through the slide can be digitally recorded, replayed, mapped and qualitatively compared between individuals. Krupinski et al. (23) have combined eye movement and slide movement observations to show subtle differences in visual search patterns between experienced and inexperienced pathologists. Treanor et al. (24) mapped the diagnostic path taken through virtual slides in three dimensions, and showed a strong relationship between the diagnostic track and diagnostic error. This throws some light on the processes involved, how eye movement, field selection and slide tracking differs from one individual to the next and how search skills can contribute to diagnostic error. It may be that measuring these basic psychovisual skills might allow us to identify 'good' pathologists early in their career.

In addition to slide movement, eye-tracking cameras also provide a valuable investigative tool in understanding how eye movement and field of view search contribute to image interpretation. Eye-tracking systems follow the movements of the pathologist's both eyes when reviewing tissue samples (Fig. 11) and have demonstrated different approaches to visual search strategies in pathology. 'Scanning' and

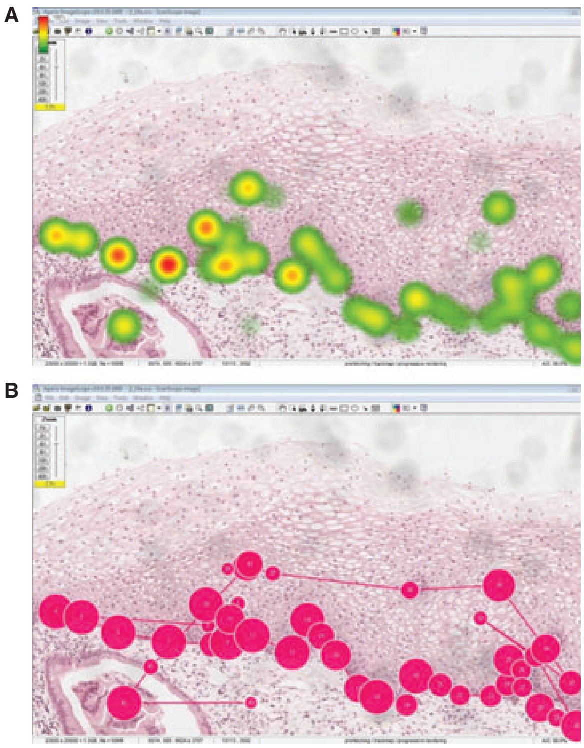

Fig. 11. Eye movement also provides a new exciting way to explore how visual acuity underpins diagnostic ability. Herein, we see the key hotspots of attention (Figure A) and search sequence (Figure B) within a single cervical histopathology image.

'selective' styles of visual search have been identified in the interpretation of cervical histopathology (25) and can lead to differences in the final diagnosis.

While these methodologies provide the tools that allow us to interrogate pathological decision-making in a more objective fashion, the reality is that we still know little about what contributes to the variation that we see in pathological diagnosis, and understand how biases, if they exist, can be controlled.

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