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Digital Cytology: a short review of technical and methodological approaches and applications.

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Digital Cytology: a short review of technical and methodological approaches and applications.

Background

By the last decade of the 20th Century digital imaging rapidly replaced film-based imaging in many medical fields. Radiology is certainly the most significant example of this technological change, but also in microscopy at the beginning of the current century it became difficult to find a conventional film camera in a Department of Pathology. Thanks to the constant increase of the power and speed of microcomputers, the year-by-year reduction in costs and their ease of use, digital cameras took their place on the head of the microscope replacing the conventional film camera.

In the same years many companies introduced on the market new instruments able to scan at microscopic level whole histological or cytological preparations and to display the resulting images by means of software which allowed the user to navigate and zoom the digital preparation as a true virtual microscope.

In the last decade this Whole Slide Imaging (WSI) technology has progressed and, despite some technical and financial hurdles and resistance to adoption, it is now frequently used in many centers for education and training, documentation, research, image analysis, quality control, second opinion and, increasingly, also for primary diagnosis. These mentioned purposes easily apply to digital histology and, with a different technical approach, they can be applied also to digital cytology [1-2].

The aim of this paper is to focus on the technical issues related to cytological WSI, to review the application of WSI, also called 'virtual slides', in cytology and to discuss its current and future use.

WSI in cytology. A 3D problem.

A histological preparation is made of a thin section of tissue with a relatively even surface lying on a glass slide and protected by a coverslip. A mounting medium stabilizes the system

and eliminates the air between the different components of the preparation.

There is not a single type of cytology. Smears and centrifuged preparations (Cytospin®) can be air-dried or fixed in alcohol or formalin based fixatives. Liquid Based Cytology (LBC) preparations are cell suspensions obtained depositing the collected cytological material in small bottles containing a preservative liquid. After fixation, appropriate instruments process the cell suspension to obtain an approximate monolayer of cells on a predetermined area of the slide. The common characteristic of the different types of cytological preparations is the irregular distribution of the cells and the possible presence of cell clusters, maximal on manual smears, minimal on some of the LBC preparations. Besides, during the drying process the cells can float in the mounting medium. In LBC the flotation is minimized, but still present. The final result is a 3-Dimensional distribution of the cytological material. This is not a problem in light microscopy because each element can be easily recognised by adjusting the fine focus control. But these structural differences between histological and cytological preparations force different scanning strategies.

Scanner focusing

The modern scanners for microscopy use different methods to calculate the best fitting focus plane while scanning a histological or cytological preparation [3-4]. Many of these methods are covered by industrial secrets, but roughly speaking there are two main methods.

The first one applies a kind of Least Squared method to calculate the ideal focus plane using an arbitrary number of focus points randomly chosen on the histological or cytological preparation. The resulting regression line should represent the best focus plane suitable for the whole preparation (Fig. 1). A second method simply divides the preparation in stripes, takes some randomly chosen focus points and assumes the mean value as generalized best fitting focus plane. These methods give acceptable or good results scanning histological slide. The standardized structure and the regular thickness of the tissue section are adequate to scan the preparation using a single z-dimension layer [5].

In cytology both methods show some limits because of the irregular distribution of the cells on the slide and because of the previously mentioned 3-D structure of the preparation. In some cases the scanner struggles to find a focus point and in some cases cannot find a focus at all. The problem can be partially solved by scanning the cytological slide at different z-stack levels and using a viewer that allows the visualization of this kind of multi level digital slides. Almost all scanners for WSI can take images from multiple z-dimension layers [6]. The user can choose the number of levels to scan and the distance between each level. The obvious result of a multi level scanning is a digital file much bigger than a file originated from a single level scanning and a longer scanning time. These technical factors: number of levels, distance between levels, dimension of the files and increased scanning time are potential sources of problems and barriers to the use of cytological WSI. The lack of agreement on them and the availability of relatively little evidence in the literature further complicates the problem.

Z-stack levels

In a recent study Bongaerts et al. [7] found that in liquid based cervical cytology the observers found a distance of 2 µm between the z-dimension layers and seven levels more acceptable than a 1µm distance. Earlier, Mori et al. [8] in a complex study based on cells dimensions determined that *"Layers of 1.5µm thickness each with a total of 10 to 15 layers resulting in 15 to 20µm scan is suitable for most cytology slides*". These findings are in contrast with Donnelly et al. [9] whose study in liquid based cervical cytology supports the use of three levels at 1µm distance between each level and Mukherjee et al. [10] who found highest inter-observer reliability, in Thyroid FNAC, for three levels scanning at 1µm distance between levels. (Table 1).

Deep Focusing

As previously mentioned, compared to the single level scanning used for a histological slide, the multi level scanning necessary in cytology creates much bigger files. A liquid based cytological preparation (about 314 mm^2) scanned at one z-dimension layer generates a file of

about 800MB - 1GB in size. The same preparation scanned at seven z-dimension layers will result in a file of 6-8 GB. This results in an increased cost for file storage. Moreover, if the virtual slide is hosted on a server to be examined online the traffic between the server and the client computer is also increased with possible delays viewing the slide. A possible solution to conjugate the microscopical details visible in a multi layers scanning with a smaller dimension of the digital file is the so-called "deep-focusing". Some examples are available. In the previously cited study [8] Mori's et al. illustrate their "focus fusion" method. This technique consists in taking the best-focused areas from each layer and building a new single level virtual slide where all the objects result in focus. A similar technology is used in the virtual slides galleries of the Eurocytology website (www.eurocytology.eu). A description of the software realised for this purpose can be found at www.cytology.cloud. A different approach to reach the same result was used by Larhmann et al. [11]. In the *Semantic Focus Point Analysis* proposed by the authors, after a complex analysis about the characteristics of the cytological preparation, specific software recognizes cells and discharges non cellular material applying a filter based on size, sharpness and colour of each detected object. This process creates a three-dimensional "master-focus layer" of the cells in the slide. Following this map the scanner selects only the images of the cells in focus and excludes blurred cells and non-cellular particles avoiding the generation of a large amount of unnecessary data (Fig. 2). One final approach would be to employ novel compression methods that discard redundant information that is replicated between z stack layers, saving only the differences between them. A similar principle is employed in video compression (e.g. MPEG encoding), where only key frames and the differences between them are saved, not the entire set of images forming the video. [12]

Digital Image Adjustment and Optimization.

It is common experience that digital images can be easily processed by means of a variety of user-friendly software. Virtual slides are composed of collections of small digital images and,

with the appropriate adjustments, can be also manipulated using the same kind of software. Quite curiously, very common issues in digital imaging like white balance, colour intensity, gamma correction, brightness etc. are not mentioned in the majority of papers published on WSI in cytology. In a very accurate review of currently available guidelines for digital pathology [13] these issues are not even mentioned. Only few papers [14] highlight the need to optimize the image quality in WSI and just a few express concerns about the possibility of manipulation in digital WSI demonstrating, for example, that manipulation of Pap-test WSI significantly affects its interpretation by cytotechnologists and cytopathologists [15]. On the other hand, improving the image quality can help in identifying some cellular features and changes otherwise difficult to recognize. While it is well recognized that the staining pattern is not only influencing interpretation but is also very much the result of the laboratory or individual cytopathologist's preferences, the ability to improve the microscopic picture quality was and still is a distinguishing expertise of the pathologist. It is not so long ago since the pathologists were perfectly able to set up a uniform Köhler illumination of a microscope or to adjust the light temperature before taking a picture with a film camera. In WSI all the technical aspects related to the image quality are apparently delegated to the manufacturer of the scanner without any control performed by the viewer. Because of the nature of the virtual slide a post-production quality control is difficult. The virtual slide, in fact, is made of thousands of small images and changing them after the scanning is scarcely feasible. Shrestha et al. [16] propose a possible solution scanning specific colour filter and verifying the reproducibility of the results in the time and between different scanners. This kind of colour calibration can be easily performed on every scanner and ensures a good constancy of the results.

Subjective perception and diagnostic accuracy.

In many studies diagnostic accuracy and subjective acceptance of cytological WSI are mutually correlated [7, 17, 18]. It is interesting to note that the diagnostic accuracy measured

as concordance between virtual microscopy and glass microscopy is usually reported as good or acceptable. At the same time a number of issues seem to affect the judgment on the subjective acceptance of cytological WSI. They can be summarized as:

- slow speed in image rendering
- occasional “freezing” of the image
- longer screening time compared to glass microscopy
- insufficient z-resolution for groups of cells.

It is quite clear that the first two points are related to the performance of the entire WSI system. The problem usually does not arise if the slide resides on the same computer where it is displayed, but normally it is hosted on a remote server connected to the local client through a Local Area Network (LAN) or via Internet. Improvement of network performance should overcome these kinds of problems in many cases.

The longer time needed for screening may be attributed both to the network speed and to the characteristics of the viewing software. The modern viewers are user friendly, but some training time is always needed. Moreover, the user must learn how to recognize the cellular features in the digital image compared to the microscope, and this may be linked to the fine difference in colours between the digital image and the microscope slide. Finally, the movement of the stage of the microscope and of the micro-focusing wheel is certainly more rapid than the virtual slide panning and z-dimension change in most cases. Improvement of the viewing software will certainly speed up the digital screening, but it is easy to imagine that for an expert cytopathologist or cytotechnologist the screening time of a conventional cytological preparation will remain shorter than the time necessary for the electronic screening of the same preparation.

The impossibility or difficulty to digitally mark cells or areas of interest is no longer a problem. All the viewers currently provided by the scanner manufacturers and by third parties allow marking and annotating the virtual slide.

Finally, the problems related to z-stacking of the virtual slide has already been discussed previously. The possibility of multi-levels scanning of the cytological slide is of fundamental importance and marks the true difference between virtual histology and virtual cytology.

Education

Intuitively, the possibility to scan whole slides and to organize them in structured databases accessible via the Internet represents a powerful teaching tool. Especially in cytology where every glass is "unique and not repeatable" examples of rare cases can be shared without risk of stain fading, glass loss or breakage. It is increasingly obvious that digital scanning can provide a more standardized setting for testing and assessing, as experienced by some National External Quality Assurance schemes in the British NHS. Moreover cytology cases are often unique and it is very difficult to provide multiple sets of exactly similar cytological preparations, typically FNA cytology rather than exfoliative cytology. A selected list of web-sites, with public or restricted access, including cytopathology teaching resources (WSI or not) is shown in Table 2. Usually they are galleries of cytological slides with or without explanatory text and/or self-assessment test. To date we are not aware of structured fully digital courses of cytology. But in times of increasing travelling costs and lack of cytological competence across health systems it is likely that this kind of teaching courses will be more necessary.

Similar considerations can be made for the proficiency test in cytopathology. Proficiency testing in cervical cytology is mandatory in USA and in many European countries. In Europe the QUATE **(**Quality Assurance, Training and Examinations Committee**)** Aptitude Test is an international examination for cytotechnologists who fulfil the criteria for accreditation in their own countries. It is designed to provide an objective assessment of a cytotechnologist's competence to screen conventional cervical smears or liquid based cytology samples and is available in traditional Papanicoloau, Surepath™ or Thinprep™ technologies. Since 2015 QUATE recommends the Eurocytology web site (www.eurocytology.eu) and its virtual slide

library as a teaching base. A QUATE mock exam is hosted in the same web site. More recently a new EU Erasmus+ funded project "Cytest" (www.cytest.eu) is providing a virtual environment for training and assessment in cytology with structured tests providing feed back to the users in all fields of cytopathology (cytest.crs4.it)

Problems related to the adoption of WSI for cytology

A number of problems can be identified reading the available literature about WSI in cytology and more in general about digital techniques applied to cytology. Many of them are the general problems related to digital pathology and generally related to the absence of a common standard for hardware and software. However, some of them are more specific for cytology. They can be briefly summarized as follow.

- Lack of clear and univocal guidelines concerning the characteristics of cytological WSI for diagnostic purposes. For example, all the recommendations reported by G Hanna et al. [11] in their recent review of contemporary guidelines in digital pathology can be applied to digital pathology as a whole without any specific indication for cytology. The recent UK Royal College of Pathologists draft document on digital pathology explicitly states "Cytopathology is considered to be out of the scope of this document, due to the lack of evidence in this specialised area. However pathologists considering the use of telepathology or digital pathology for cytological diagnosis could use the guidance in this document as a basis for establishing safe practice." [19]

- Lack of commitment of the major manufacturers of scanners in the specific cytological field. To date we are aware of only one specific scanner for cytology (Leica-Aperio CSO™). This instrument can scan a cytological slide at very high magnification (up to oil immersion 100x), while the others have a maximum magnification of 40x. Unfortunately no information is provided about the time necessary to perform such high resolution scanning, though it is likely to be longer than a corresponding 20x or 40x scan, with concomitant larger file size.

- Lack of agreement on the scanning resolution required for cytology. It is surprising that most of the published studies do not mention the magnification used. Expressions like “high-resolution scanning” or “highest possible resolution” are widely used, but an exact specification is often missing. In fact, this information can be inferred from the scanner brand (if specified). As previously mentioned only the Leica-Aperio CSO provides magnification higher than 40x using oil immersion.

- Lack of agreement on z-stack resolution. This is probably the core problem of WSI in cytology and the main difference between histological and cytological WSI. It is common experience that fine focusing is often used in screening of a conventional cytological preparation. Hence increasing the number of z-levels should lead to better results screening a digital slide. As previously seen, this intuitive concept is not completely supported by the available data and, if assumed as true, it opens new problems such as the increase in disk space required - with related increase of the costs and a longer screening time. A single, reliable and effective solution to all these issues does not exist, but at least two alternative solutions can be explored. The first concerns the development of new and more effective software to collect in a single z-level virtual slide all the information resulting from a multi z-levels scanning. In this regard the previously mentioned *Semantic Focusing* is a promising software development that needs more extensive validation studies, but traces an original new route to face the problem. Unfortunately, for what we know, it is related only to a specific scanner and it is not commercially available. The second way is hardware related. Nowadays all the scanners can perform multi z-levels, but the total scanning time is close to the result of the time necessary to scan a single level multiplied by the number of levels. This means that a fast scanner takes about 5 minutes to scan a ThinPrep™ preparation (i.e. an area of about 20x20 mm) at 7 z-levels. The same scanner takes less than a minute (about 50 seconds) to scan a single level of the same area. A different approach based on the real-time detection of multiple focus points on different levels would significantly decrease the scanning time.

Conclusions

Cytology is an often overlooked area when whole slide imaging is considered in a laboratory, due to understandable barriers such as the complexity of scanning multiple z-stacks and consequent time and storage costs. However given the ongoing need for cytological diagnosis (a trend which may possibly increase in future as minimally invasive procedures to obtain material for genetic/ molecular analysis are used) together with a shortage of suitably trained cytopathologists, it is likely that the need for WSI in cytology may increase, and hardware/ software solutions to the barriers will be sought.

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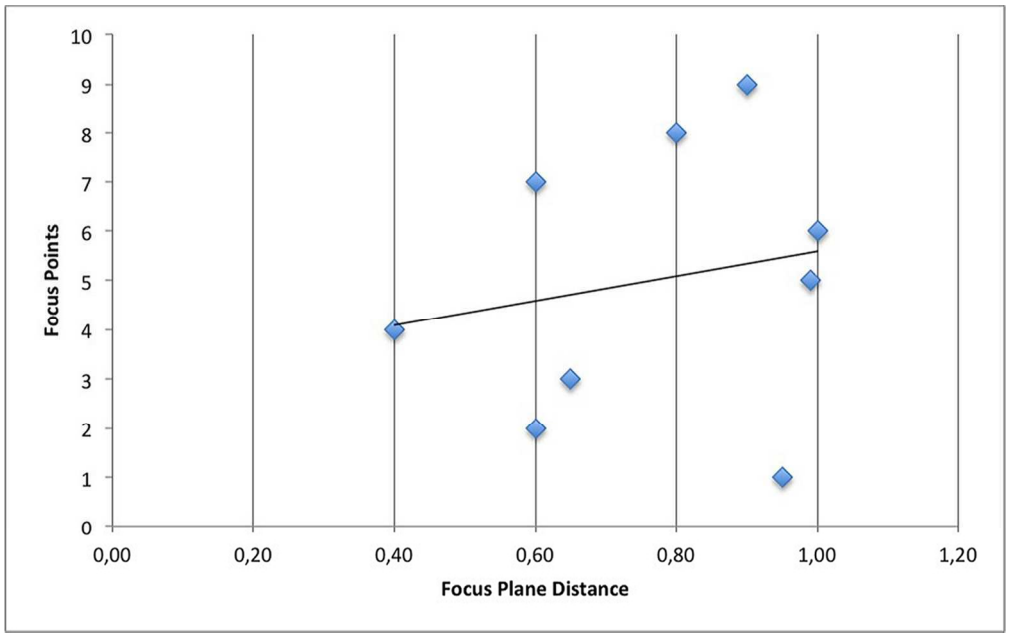
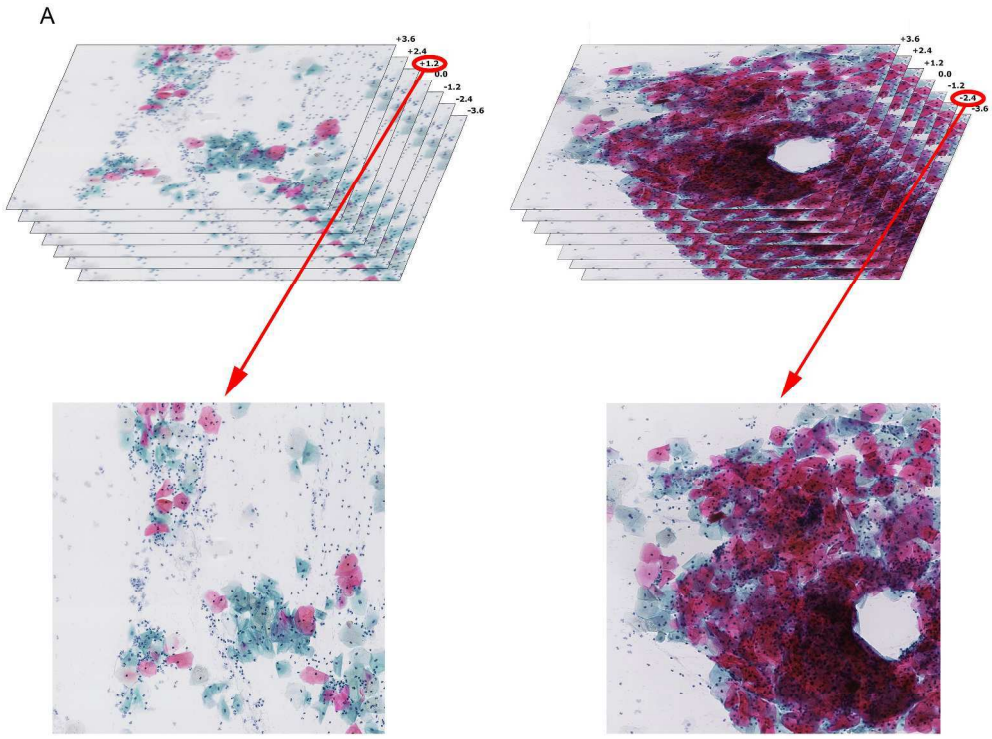


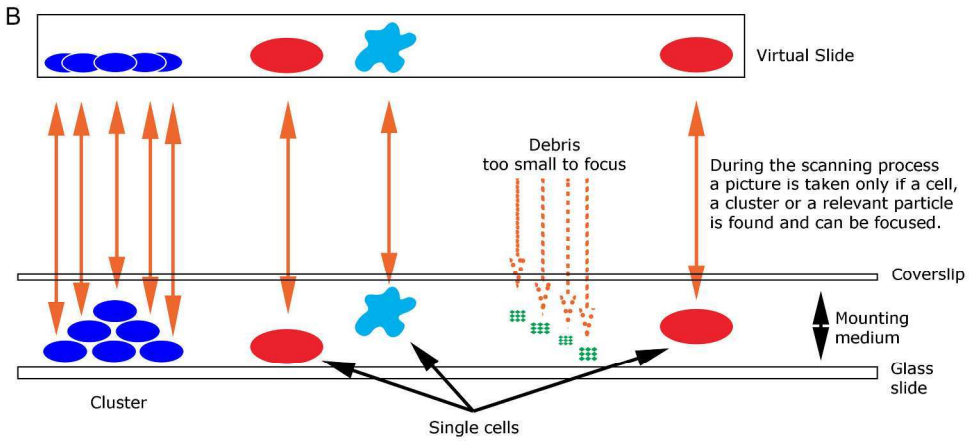
Least Squared Method between a number of randomly chosen focus points and their distance from the focus planes. The resulting best fitting line should represent the ideal focus plane for the whole slide.

102x64mm (300 x 300 DPI)



A. The traditional approach consists in taking a picture (tile) for every single level at a predetermined distance between the levels (in the example: 1.2mμ). Because of the high number of possible tiles in each level (in some cases they can be some hundred thousands) the virtual slide file will be very big (see text).

846x692mm (96 x 96 DPI)



B. In the Semantic Focusing approach a picture is taken only if a cluster, a cell or a relevant particle is found during the multi-level scanning. The obtained virtual slide will result in a considerably smaller file.

792x365mm (150 x 150 DPI)

Reference	Domain	Sample size (n)	Recommended z stacks	Distance between layers	Comment
Bongaerts et al. (7)	Gynae liquid based	47	7	Initially 1mμ changed to 2mμ	Participants found more informative the 2mμ interval
Mori et al. (8)	Breast FNAC	not stated	10-15	1.5mμ	The number of layers is determined by a study on cells dimension
Donnelly et al. (9)	Gynae liquid based	192	3	1mμ	The main problem was the difficulty to focus through the clusters
Mukherjee et al. (10)	Thyroid FNAC	12	3	1mμ	The study was done on 3, 5 and 7 layers. The best agreement was obtained on 3 layers virtual slides

Table 1. Recommended z-stack layers and distance between layers in different studies.

WEB site address	Society / Institution / Authors	Purpose	Target groups	Imaging: static/ virtual slides (vs)
http://www.bsccp.org.uk/	The British Society for Colposcopy and Cervical Pathology (BSCCP)	The aims of the Society are: to provide professional advice concerning the practice of colposcopy, screening for cervical pre-cancer and cancer, to promote best standards of practice in colposcopy, to facilitate the dissemination of information about colposcopy to the general public …	Public Cytologists	Static
http://www.eurocytology.eu	Part of the EU Leonardo Lifelong Learning Programme. Several international Partners.	The Eurocytology website is a unified platform for the vocational training and professional education of cytotechnologists and cytopathologists engaged in all aspects of clinical cytology screening and diagnosis.	Cytopathologists Cytoscreeners Trainees	Static and vs
http://www.cytest.eu/	Cy-TEST Cytological Training at European Standards through tele pathology. Several European Partners.	Cy-TEST focuses on the area of Cytology, intended for the screening and diagnosis of cancers. The aims of Cy-TEST System are: training and performance Aptitude test exams; training pathology residents; continuing Medical Education courses and specific activities during meetings.	Cytoscreeners Biologists Pathologists	Static and vs

http://www.cytology-asc.com/	Australian Society of Cytology (ASC)	The primary aims of Australian Society of Cytologists (ASC) are to foster an interest in the training, status and conditions of employment of cytologists within the Commonwealth of Australia, to achieve uniformity in the interpretation and reporting of cytological findings, and to advance the knowledge and standards of clinical, diagnostic and general cytology.	Cytologists	Static and vs
http://www.cytology-iac.org/ http://www.cytology-iac.org/educational-resources/virtual-slide-library	The International Academy of Cytology (IAC)	The IAC is an organization of cytotechnologists devoted to creating an international network of recognized experts in the field of cytopathology through the exchange of knowledge and experience on a global basis.	Public Cytopathologists	Static and vs
http://www.cytologystuff.com/	Hologic	CytologyStuff is an educational service provided to cytotechnologists, pathologists and other professionals by Cytyc Corporation, Boxborough, MA. This web site is composed of 4 parts: Study; Watch; Learn; Interact.	Pathologists	Static
http://www.cytopathology.org/	American Society of Cytopathology (ASC)	The ASC is the principal conduit for dissemination of research findings relevant to the practice of Cytopathology. National professional society of physicians, cytotechnologists and scientists dedicated to the cytologic method of diagnostic pathology.	Public Cytopathologists	Static
http://www.cytology.cloud/gk/	Dr. G.Kocjan, Dr. A.Capitanio	A workshop on Salivary Gland Cytology	Cytopathologists Trainees Cytoscreeners	vs

http://www.papsociety.org/index.html	Papanicolaou Society of Cytopathology (PSCO)	This Committee seeks to develop companion scientific programs at other regional pathology societies.	Public Pathologists Practitioners Trainees	Static
http://www.tasteproject.eu/	Telepathological Assessment of histopathological and cytological Techniques (TASTE)	This project has been funded with support from the European Commission.	Pathologists: practitioners and trainees	Static
http://www.uscap.org/	The United States and Canadian Academy of Pathology (USCAP)	The USCAP is an organization devoted to providing pathologists new and updated information, as well as ways of reinforcing that knowledge, in there are(s) of interest and expertise in the field of human disease.	Public	vs
http://www.viewsiq.com	ViewsIQ	ViewsIQ is an imaging software company that develops microscopy imaging solutions	Photographers	vs
https://bethesda.soc.wisc.edu/ http://nih.techriver.net/	ASC - Bethesda System Reporting Gynaecologic Cytology 2014. This site and the print atlas represent the work of a large number of people from private, public and academic facilities.	The purpose of this ATLAS is to offer instructive images with explanatory text to illustrate the features of the BETHESDA System. This site will provide an opportunity for real-time updates of terminology and criteria.	Pathologists: practitioners and trainees.	Static
http://icytology.wordpress.com/	iCytology.wordpress.com	Case reports	Pathologists	Static
http://pathhsw5m54.ucsf.edu/introduction.html	Warnock ML and McCowin MJ	Cases illustrating pathological and radiographic changes of disease. A clinical summary will be followed by description of pertinent radiographs and images of the histology. Based on these, the viewer can formulate a diagnosis and compare it to that given in the following discussion.	Pathologists	Static

http://pathorama.ch/	Idea and concept: Dr Glatz-Krieger K and Dr Glatz D; Contributing partners: Wey R and Boerger C, Institute for Clinical Pathology, University if Zurich; Several Sponsors.	Pathorama is a freely accessible e-learning and information platform for people interested in surgical pathology. Pathorama provides you with high quality images and virtual slides for teaching and self-instruction covering a wide range of topic in all subspecialities of surgical pathology and cytology. Various courses, slide seminars, quizzes, and learning games for students, surgical pathologists, and cytopathologists are available.	Medical students Surgical pathologists Cytologists Health care professionals Sender of biopsies	Static and vs
http://screening.iarc.fr/	IARC Screening Group WHO	SCR rational: Screening for cancer implies testing for early forms of disease before symptoms occur. The major studies are on cervical cancer, oral cancer and breast cancer.	Pathologists These courses were designed for medical staff of all levels	Static
http://www.virtualpathology.leeds.ac.uk/slides/	Leeds University	Probably the richest virtual slides library in the world	Pathologists Trainees	vs
http://137.189.150.85/cytopathology/	Cytology Website	This website is intended for the professional education of cytotechnologists	Cytologists Laboratory personnel	Static