PATHOLOGICA 2023;115:127-136;
DOI: 10.32074/1591-951X-868

Review

The slow-paced digital evolution of pathology: lights and shadows from a multifaceted board

Alessandro Caputo[1,2], Vincenzo L'Imperio[3], Francesco Merolla[4], Ilaria Girolami[5], Eleonora Leoni[6], Vincenzo Della Mea[7], Fabio Pagni[3], Filippo Fraggetta[2]

[1] Department of Pathology, Ruggi University Hospital, Salerno, Italy; [2] Pathology Unit, Gravina Hospital Caltagirone ASP, Catania, Italy; [3] Department of Medicine and Surgery, Pathology, University of Milan-Bicocca, IRCCS Fondazione San Gerardo dei Tintori, Monza, Italy; [4] Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Campobasso, Italy; [5] Department of Pathology, Provincial Hospital of Bolzano (SABES-ASDAA), Bolzano-Bozen, Italy; Lehrkrankenhaus der Paracelsus Medizinischen Privatuniversität; [6] Pathology Unit, Busto Arsizio Hospital, Busto Arsizio, Italy; [7] Department of Mathematics, Computer Science and Physics, University of Udine, Udine, Italy

Summary

Objective. The digital revolution in pathology represents an invaluable resource fto optimise costs, reduce the risk of error and improve patient care, even though it is still adopted in a minority of laboratories. Barriers include concerns about initial costs, lack of confidence in using whole slide images for primary diagnosis, and lack of guidance on transition. To address these challenges and develop a programme to facilitate the introduction of digital pathology (DP) in Italian pathology departments, a panel discussion was set up to identify the key points to be considered.

Methods. On 21 July 2022, an initial conference call was held on Zoom to identify the main issues to be discussed during the face-to-face meeting. The final summit was divided into four different sessions: (I) the definition of DP, (II) practical applications of DP, (III) the use of AI in DP, (IV) DP and education.

Results. Essential requirements for the implementation of DP are a fully tracked and automated workflow, selection of the appropriate scanner based on the specific needs of each department, and a strong commitment combined with coordinated teamwork (pathologists, technicians, biologists, IT service and industries). This could reduce human error, leading to the application of AI tools for diagnosis, prognosis and prediction. Open challenges are the lack of specific regulations for virtual slide storage and the optimal storage solution for large volumes of slides.

Conclusion. Teamwork is key to DP transition, including close collaboration with industry. This will ease the transition and help bridge the gap that currently exists between many labs and full digitisation. The ultimate goal is to improve patient care.

Key words: digital pathology, artificial intelligence, computational pathology, education

Received: April 3, 2023
Accepted: April 04, 2023

Correspondence
Filippo Fraggetta
Pathology Unit, Gravina Hospital, via Portosalvo 1, 95041Caltagirone, Italy
E-mail: filippofra@hotmail.com

How to cite this article: Caputo A, L'Imperio V, Merolla F, et al. The slow-paced digital evolution of pathology: lights and shadows from a multifaceted board. Pathologica 2023;115:127-136. https://doi.org/10.32074/1591-951X-868

Introduction

The adoption of digital pathology (DP) into pathology laboratories represents a significant shift in the routine work. This change affects all workstations and involves more than just converting glass slides to Whole Slide Images (WSI), as some might have mistakenly assumed. As discussed in the recent literature [1-4], the implementation of DP involves a fully tracked and automated pathology workflow, as well as the standardisation and interoperability of processes with the potential use of artificial intelligence (AI) tools for primary diagnosis with WSI. A gradual integration of hardware [5] and software [1,6] modifications and the implementation

of quality control (QC) checkpoints [2,7] during sample processing can ease the transition to DP. Although some guidelines and recommendations exist [8], few pathology departments have completed a full transition to DP [9-11], in Italy like in the rest of the world. Start-up costs, lack of confidence in using WSI for primary diagnosis, and lack of transition guidance are barriers to adopting DP [12]. To address these challenges and identify the key points for a transition to DP in Italian pathology departments, a panel discussion was launched.

Meeting overview

A preliminary web call was held on July 21, 2022, via Zoom to determine the most critical topics to be discussed during the in-person meeting. The call included the participation of young pathologists and residents, senior and expert pathologists with different skills in digital pathology, as well as a computer scientist from different parts of Italy, stressing the multidisciplinary approach to the panel discussion. During this call (Fig. 1), the participants decided to structure the final meeting into four different sessions, as follows:

- Session I focused on the definition of digital pathology, ranging from a narrower interpretation as simply capturing WSI to a broader holistic concept impacting the traditional pathology workflow.
- Session II focused on the clinical use of DP and a list of the possible areas of application included: primary histological and cytological diagnoses, telepathology (second opinion), quality assurance and computer-assisted pathology.

Figure 1. The participants to the preliminary web call held in Zoom. Left to right, top to bottom: Fabio Pagni, Filippo Fraggetta, Eleonora Leoni, Alessandro Caputo, Vincenzo della Mea, Vincenzo L'Imperio, Francesco Merolla, Anna Maria Pisano (from the provider Global Studio) and Ilaria Girolami.

- Session III explored the use of AI for prognostic/predictive purposes, as well as ethical implications and explainability.
- Session IV introduced the educational aim of DP as a next generation tool in teaching programs.

Session highlights

Session I: Definition and scopes

DP involves digitising and analysing glass slides using a WSI scanner and image viewer. However, this definition is limited and does not fully capture its scope [13]. The European Society of Digital and Integrative Pathology (ESDIP) recommends reimagining DP as a holistic approach that includes interventions at all stages of work in the pathology laboratory, introducing and supporting innovation [14]. This transition can include a fully tracked and automated workflow [1,6] starting even before the sample arrives at the pathology department, with the integration of the pathology laboratory information system (LIS) with the hospital's Electronic Medical Record (EMR) Software [15] and the use of 2D barcodes for automated, paperless sampling [6]. Subsequent phases, such as grossing and archiving, can also be tracked and automated using macro capture cameras, speech-to-text devices, barcodes and BlocDoc [2,16,17]. The selection of the appropriate scanning device for routine diagnostics should be based on the specific needs of each department [7,18], such as workload and field of interests. The first variable may impact the choice of the entry level rack size, while the proportion of specific sub-speciality (i.e. prevalence of cytopathology) might require the need for Z-stack or extended focus options (Tab. I). While DP offers the potential to reduce human error [19], it also raises unresolved questions, such as the lack of specific regulations for virtual slide storage [20] and the optimal storage solution for large volumes of slides. The successful implementation of DP requires the involvement of the entire pathology team, including IT service, technicians, biologists, and molecular and computer scientists.

Finally, before going digital, it is essential to carefully analyse and possibly redesign the routine workflow and address potential issues with IT systems, including performance, storage options and costs, and emergency backup procedures.

Session II: Specific applications

Primary histological and cytological diagnosis

The non-inferiority of WSI for primary histological diagnosis compared to glass slides has already been

Table I. Some of the most adopted scanner devices on the market in Europe.

Manufacturer	Model	Imaging mode(s)	Max Slide capacity	Scan speed*	Objective	Image capture magnification	Image capture resolution**	Digital slide format	Multilayer support	Barcode support	Special features
Leica	Aperio GT 450 DX	Brightfield	450	40x: 32 sec	Custom optics by Leica Microsystems for native 40x scanning with 1 mm FOV	40x	40x: 0.26	SVS, TIFF DICOM	-	1D, 2D	Continuous loading; automatic image control
Philips	IntelliSite Ultra-Fast Scanner	Brightfield	300	40x: 60 sec	Olympus, NA 0.75 Plan Apo	40x	40x: 0.25	RAW, iSyntax DICOM	-	1D, 2D	FDA approved
3DHistech	Pannoramic 1000	Brightfield	1000	40x: 32 sec	20x, NA 0.8, Plan-Apochromat	40x	40x: 0.25	DICOM, MRXS	Optional multilayer (Z-stack) and extended focus scanning	1D, 2D	Continuous loading; flexibility (arbitrary scanning)
					40x, NA 0.95, Plan-Apochromat,	80x	80x: 0.12	DICOM, MRXS	Optional multilayer (Z-stack) and extended focus scanning	1D, 2D	Continuous loading; flexibility (arbitrary scanning)
					40xw, NA 1.2, C-Apochromat	80x	80x: 0.12	DICOM, MRXS	Optional multilayer (Z-stack) and extended focus scanning	1D, 2D	Continuous loading; flexibility (arbitrary scanning)
Hamamatsu	NanoZoomer S360	Brightfield	360	40x: 30 sec	20x NA 0.75	20x - 40x	20x: 0.46	NDPI, DICOM(?)	Z-stack available	1D (standard feature), 2D (optional)	Automatic image confirmation
							40x: 0.23				
Olympus	VS200	Brightfield, Darkfield, Phase Contrast (optional), Simple Polarization (optional), Fluorescence (optional)	210	20x: 90 sec	10x NA 0.4	2x, 4x, 10x, 20x, 40x, 60x, and 100x	10x: 0.548	vsi, JPEG, and TIFF	Z stack imaging, extended focus imaging (EFI)	1D, 2D	RUO
					20x NA 0.8		20x: 0.274				

established [21-25]. Any issues encountered during implementation can be addressed by streamlining the workflow [1,12]. The application of digital technologies can reduce errors and lead times at every process stage. In contrast, primary cytological diagnosis has lagged behind histology due to several factors [26-29], like the three-dimensional nature of cytological specimens, which can make it difficult to capture all diagnostic information with the single-slice focus approach. New instruments implement extended focusing or Z-stacking to solve this problem [30], but this can result in longer scan times longer scan times and possibly larger WSI file sizes. Different cytological preparations are more or less subject to these issues, with liquid-based cytology showing the best performance [31]. Improvements in primary diagnostics also include the ability to archive a slide's morphology for legal purposes [32] and then use the biological material for molecular testing, which is particularly important for cytological material.

Telepathology and second opinion

Telepathology was one of the first uses of DP [32] with numerous advantages: i) multiple people can view the slide at the same time, ii) globally in seconds, and iii) adding detailed annotations. Sharing slides for second opinion purposes may reduce friction and costs. However, careful legal regulation still needs to be improved, and the international society should define the appropriate limits of its use. A further application of telepathology was started in underdeveloped countries to supply the absence of specialists or support local pathologists in their learning curve [34].

Quality assurance

DP can be used for external quality control by automatically sending random cases for review. Internal review of cases can also be automated via the laboratory information system without manually identifying and retrieving cases. The quality assurance process is made possible by instant sharing and concurrent WSI access without having to move slides [25] physically. DP can also facilitate cyto-histological correlation, as demonstrated in cervical cancer screening [30], optimising costs and effort involved [30,35]. In addition, a streamlined workflow with barcodes and barcode readers significantly reduces laboratory errors [36] such as identify and mix-up problems [1]; transcription errors can be avoided with automated printers, and reading and matching errors thanks to the integration of patient information, gross images, BlocDoc images and digital slides on the same page through Laboratory Information System [2]. Finally, DP can improve reproducibility and accuracy in tasks such as estimating the percentage of Ki-67-positive cells or evaluating PD-L1

Table I. *continues.*

Manufacturer	Model	Imaging mode(s)	Max Slide capacity	Scan speed*	Objective	Image capture magnification	Image capture resolution**	Digital slide format	Multilayer support	Barcode support	Special features
Olympus					40x NA 0.95		40x: 0.137				
					60x NA 1.42 (oil)		60x: 0.091				
					100x NA 1.45 (oil)		100x: 0.055				
					Also available: 2x, 4x						
Ventana	DP 600	Brightfield	240	20x: 36 sec	Nikon 20x apo NA 0.75	20x - 40x	20x: 0.465	DICOM, BIF, TIF	Z-stack available	1D, 2D	EU CE-marked IVD
							40x: 0.25				

*Scanning speeds listed are for 15 mm × 15 mm area (brightfield); **Resolutions listed are in µm/pixel.
Abbreviations: 1D, one dimensional; 2D, two dimensional; WSI, whole slide imaging

immunohistochemistry [37,38] by automatic validated web-based tools.

Computer-assisted diagnosis

Computer-assisted diagnosis (CAD) can only be used effectively when a significant part of routine histology is digitised. CAD plays a key role developing and exploiting biomarkers and integrating multi-omics data. Machine learning can be used for a range of CAD applications, from leveraging WSIs and cell detection tools to speed up tasks like cell counting [39] to comprehensively analyse a WSI and generate a diagnosis, speeding up the diagnosis and improving its accuracy [40,41]. Other systems can identify and highlight specific features, saving time for the pathologist who would otherwise have to search for them [42]. Finally, AI-CAD tools can also be used to screen large batches of cases after scanning and triaging them: positive or suspicious cases can be prioritised and shown first to the pathologist to ensure faster turn-around times for these time-sensitive diagnoses.

Computer scientists and AI researchers, working closely with pathology labs, can be valuable members of the digital pathology team and work with private companies to develop AI-based tools. However, a lack of regulations in this area is currently preventing the full integration of these specialists into the pathology team, which should be tackled at the institutional level in the future. Some international digital societies (e.g. Digital Pathology Association) have already defined the use cases for this engagement, defined the stakeholders' roles, and discussed this partnership's opportunities and pitfalls [43]. There are already several examples of this fruitful collaboration in different scenarios, such as in the case of BigPicture. This public-private partnership brings together a wide range of expertise from academic institutions, SMEs, public organisations, pharmaceutical companies and an extensive network of partners contributing images [44]. Another example is PathLAKE, a consortium that includes some of the UK's leading digital and computational innovators from the National Health Service (NHS) and academia and has led to the creation of a computational pathology hub with to create the world's largest repository of annotated digital WSI [45].

Session III: Digital Pathology and Artificial Intelligence, two sides of the same coin

Pathology increasingly involves computer science and, in particular, the use of various AI tools [46] (Tab. II). Computer scientists are developing new AI tools to improve diagnostic accuracy and identify novel biomarkers for precision oncology. For example, the subjective nature of histopathological analysis due to differences in visual perception and data integration between observers can be addressed by automated AI-based extraction of multiple sub-visual morphometric features on H&E-stained slides, leading to the birth of "pathomics" [47].

AI for diagnosis

The possible improvement in the real world of routine diagnoses ranges from cancer to non neoplastic pathology, with a myriad of different attempts, only in part

Table II. Definitions of the different terms used in computational pathology.

	Definitions
Artificial Intelligence (AI)	The theory and development of computer systems able to perform tasks that normally require human intelligence, such as visual perception, speech recognition, decision-making, and in general problem solving.
Machine Learning (ML)	Subfield of AI devoted to software or machines that improve the performance of tasks through exposure to data (e.g., a training set) and experience, without being explicitly programmed to solve such tasks.
Artificial Neural Network (ANN, NN)	Systems inspired by the architecture of human and animals brains. As such, they include simulations of neurons, connected by synapses. Neurons are usually organised in layers: one for input, one for output, and a variable number of hidden layers in the middle. NNs are one of the ways machine learning is implemented.
Deep Learning	Subfield of machine learning, whose systems are characterised by the use of multiple layers to extract higher and higher level features from the input. The implementation usually occurs by means of NNs with many layers.
Convolutional Neural Network (CNN)	Convolutional neural networks are a type of deep neural networks where layers implement convolutional filters, particularly designed for image classification, object detection, etc.
Generative Adversarial Network (GAN)	ML model for generation of data (text, images, etc) in which two neural networks are trained at the same time: one to mimic the images of the training set, the other to recognise whether the generated images are real or fake. Recent evolutions also allow classification through GANs.

effective [49,49]. Both supervised machine learning models and CNN-based approaches [48] can be used to discriminate between benign and malignant tumours. An interesting and translational application regards deep CNNs trained on images of skin lesions to be complementary associated to histological data [50]. These methods have the potential to be approved for use in clinical practice and often focus on common and impactful cancers such as breast and prostate cancer and melanocytic lesions. In parallel, AI can aid and augment pathologists in the evaluation of non-neoplastic diseases by helping in discrimination of entities, quantification of immunohistochemistry, and 3D reconstruction [7,51-53].

AI for prognosis

AI approaches have been used to predict clinical outcomes based on the spatial arrangement and architecture of different tissue elements. For example, research has shown that a graphical-derived computed feature based on the spatial distribution and type of tumour infiltrating lymphocytes (TILs) can be more accurate at predicting outcomes than TIL density alone in cancers such as non-small cell lung cancer and triple-negative breast cancer [54-57].

AI for prediction

Pathologists are increasingly being asked to assess biomarkers as companions to therapy delivery, with programmed death ligand 1 (PD-L1) being one of the most common. AI on WSI was used to train a deep learning method (DL) to automatically score PD-L1 expression in images of non-small cell lung cancer biopsy samples [58]. Predicting genetic composition from WSI is a promising area, with some initial positive results in specific settings (e.g. microsatellite instability) [59] and others with less clinical focus and more speculative development (e.g. translocations [60].

Ethics and AI: what's the role of explainability?

The concept of explainability, or the need for an explanation of how and why the system reached certain conclusions in a complex decision support task, is important in medicine because physicians need to understand the rationale behind a particular diagnosis or treatment recommendation [61,62]. Moreover, most recent advances in this field have shown the capability of AI in detecting surrogate phenotypic modifications underlying genetic alterations, potentially easily assessable through a microscope. These AI techniques, such as reverse engineering and explainability tools, can identify previously underestimated histological features, such as laminated fibrosis and clear tumour cells associated with HRD [63] and a low tumour-to-stroma ratio, which may be a novel characteristic of the no specific molecular profile (NSMP) endometrial carcinoma molecular class [64]. Several definitions have been proposed to characterise the explainability of AI in medicine, which could also apply to pathology, focusing on the intersection of interpretability, understandability, ease of use, and utility [62]. Different pathologists need different explanations to trust an algorithm, and requests from clinicians as end-users can differ from those from regulators and government agencies. Collaboration between AI researchers, pathologists, clinical colleagues, IT collaborators, private companies, and representatives of national health authorities is crucial for the development and implementation of AI in a way that balances the advancement of knowledge with ethical concerns such as patient data security, avoidance of discrimination, and competing interests.

The lab of the future: what to expect from AI?

Indeed, the application of AI to the text-to-image translation domain is giving rise to different algorithms available online and capable of translating the text to newly generated images, as in the case of DALL-E (https://labs.openai.com/) or stable diffusion tools (e.g. Lexica, https://lexica.art/). In particular, asking these tools to visualise "The lab of the future: what to expect from AI" what has been obtained is reported in Figure 2. It is interesting to note the different viewpoints enhanced by the two algorithms, the first highlighting the "integrative" role that AI can have in our practice by networking the different aspects of our routine work (from clinical data and images to molecular and omics bid data), as opposed to the more workflow-centred representation of the second, showing the perspective of a fully integrated and tracked laboratory system. In this sense, it is expected that pathology laboratories will increasingly rely on AI-based automation in the future. This could include monitoring diagnostic algorithmic results, using AI for quality assurance of laboratory data, and automated assessments in large-volume clinical trials [65]. While some AI techniques are beginning to outperform humans at specific image-based tasks, pathologists should not fear being replaced by AI as true human-like AI is unlikely to become a reality in the next few decades [66,67]. Instead, AI in pathology offers pathologists the opportunity to expand the scope of their practices and become more integrated into overall patient care [65]. In this setting, recently, 24 international experts in computational pathology unanimously agreed that AI would be routinely and impactfully used within pathology laboratories by

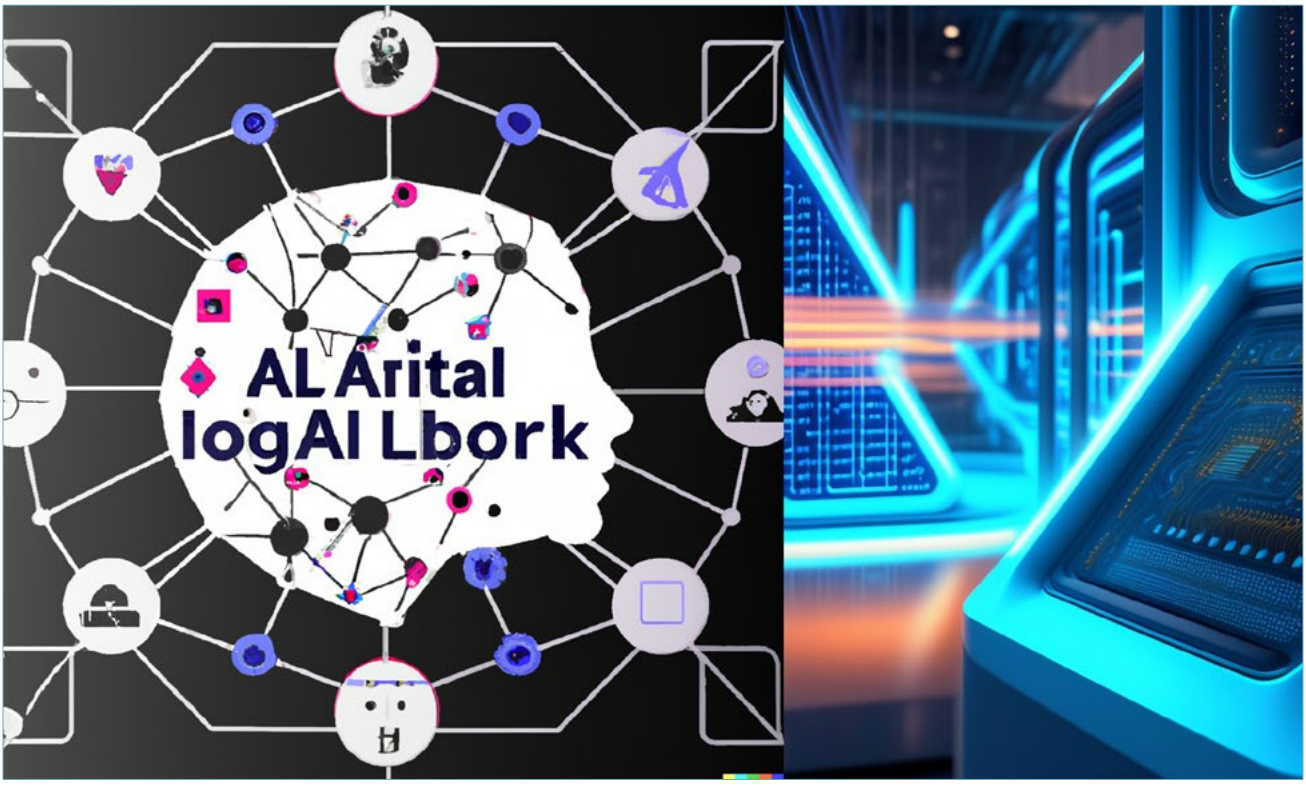

Figure 2. Images generated through online-available algorithms for text-to-image generation, such as DALL-E (https://labs.openai.com/) on the left and stable diffusion (https://lexica.art/) on the right, with the prompt "The lab of the future: what to expect from AI".

2030, with significant influence on key performance indicators (KPIs), pathology workforce and specific pathologist/technician tasks, as well as specific AI applications, integrated and automated diagnostics, regulatory/legal and ethical aspects [68].

Session IV: Educational aspects of digital pathology

Digital pathology can be used to enhance pathologist education by providing access to annotated and clinically data-rich WSIs that multiple people can view at the same time. It can also help overcome technophobia among senior pathologists by providing appropriate training [69] and can provide up-skilling through virtual lectures, as demonstrated by the recent experience of the COVID-19 pandemic [70]. Digital pathology can also provide opportunities to learn about rare pathology cases and improve diagnostic accuracy by sharing digital image databases between hospitals. It can also generate virtual atlases and specific collections for exceptional series, adding a dynamic and interactive experience. On the other hand, proper digital pathology usage requires knowledge about it. Thus it has to become part of the curriculum for Pathology residents and other involved professions, like laboratory technicians, biology and computer scientists, and IT managers [71].

Conclusions

For a successful transition to digital pathology, it is crucial that all professionals involved, including those from the industry, actively work together and understand the missing elements that need to be addressed. Multidisciplinary work will ease the transition and help bridge the gap between many labs and full digitization. The ultimate goal is to improve patient care (Figure 3). Moreover a widespread use of DP in routine practice may change our daily professional lives [72,73]. In this way, technology can bring people closer together instead of separating them and undermining their humanity. DP can represent a possible solution to cover shortfalls in staffing due to retirement/maternity and carer leave, long-term sick leave, and so on, as already demonstrated by the UK experience [74].

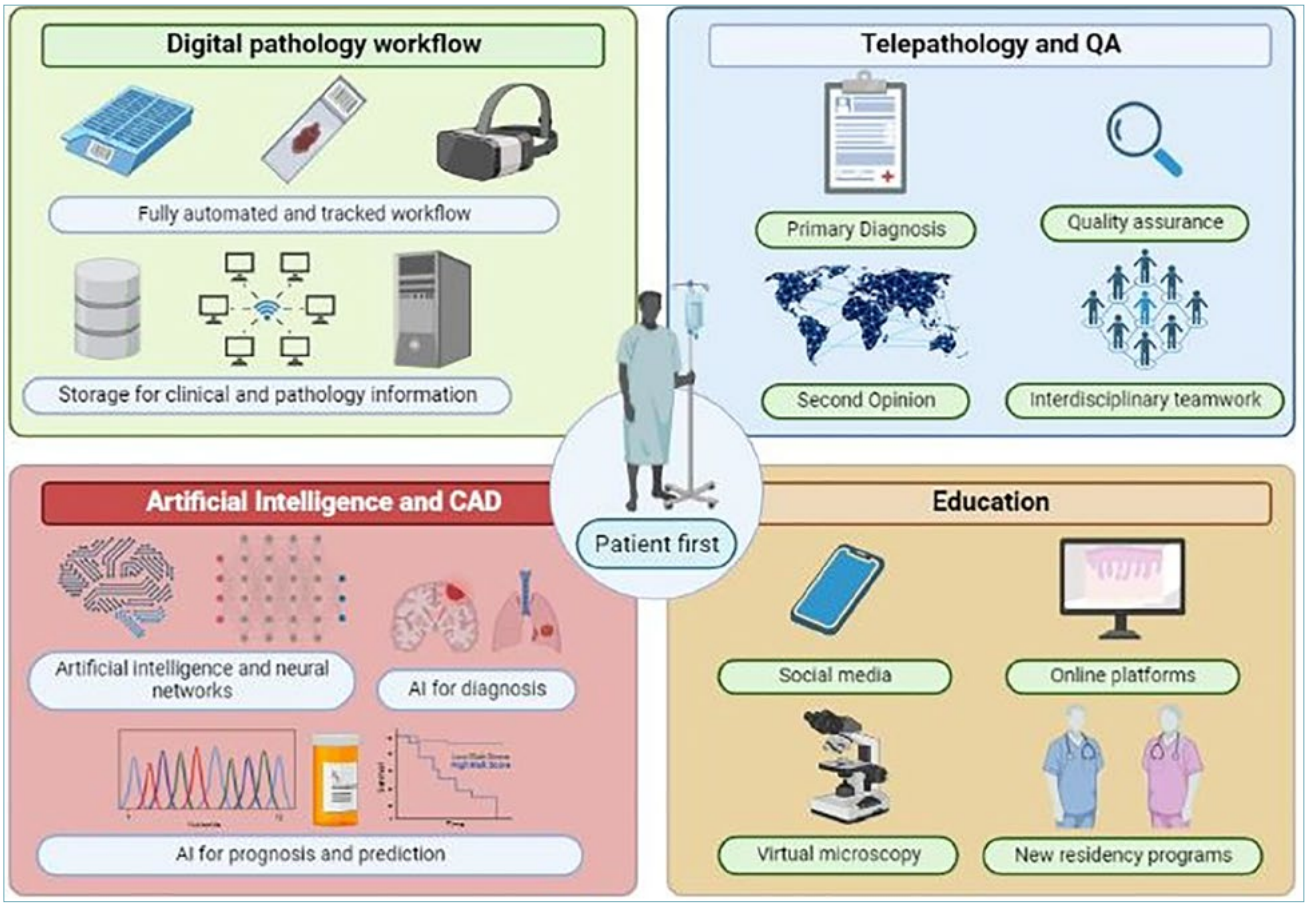

Figure 3. The image summarises the different sides and possible implications of the adoption of digital pathology.

Acknowledgements

We would like to thank the organisers from Roche and the provider (Global Studio) for the realisation of the meeting and for facilitating fruitful discussion.

Conflicts of interest

The authors received fees by Roche for participation. Fraggetta F. is one of the inventors of "Sample imaging and imagery archiving for imagery comparison Merlo PT et al. US patent 16/688/613 2020."
All authors declare that they have no other competing interests in connection with this article.

Funding

Prof. Fabio Pagni and Dr. Filippo Fraggetta participated in the preparation of the paper during their collaboration "Diplomat" project- PNRR Next Gen Eu PNRR-MR1-2022-12375735. Vincenzo L'Imperio included the paper in the University Milan Bicocca "Dipartimento di Eccellenza 2023-2027 Impact Medicine project".

Authors' contributions

All authors contributed equally to the conception, drafting, and editing of the manuscript.

Ethical consideration

Ethical approval was not sought due to the non-experimental nature of the present work.

References

1 Fraggetta F, Caputo A, Guglielmino R, Pellegrino MG, Runza G, L'Imperio V. A Survival Guide for the Rapid Transition to a Fully Digital Workflow: The "Caltagirone Example." Diagnostics (Basel) 2021;11. https://doi.org/10.3390/diagnostics11101916

2 L'Imperio V, Gibilisco F, Fraggetta F. What is Essential is (No More) Invisible to the Eyes: The Introduction of BlocDoc in the Digital Pathology Workflow. J Pathol Inform 2021;12:32.

3 Caputo A, Gibilisco F, Belmonte B, Mondello A, L'Imperio V, Fraggetta F. Real-world digital pathology: considerations and ruminations of four young pathologists. J Clin Pathol 2023;76:68-70.

4 Pisapia P, L'Imperio V, Galuppini F, et al. The evolving landscape of anatomic pathology . Critical Reviews in Oncology/Hematology. 2022;178:103776. https://doi.org/10.1016/j.critrevonc.2022.103776

5 Hanna MG, Pantanowitz L. Bar Coding and Tracking in Pathology . Surgical Pathology Clinics 2015;8:123-35. https://doi.org/10.1016/j.path.2015.02.017

6 Fraggetta F, Garozzo S, Zannoni GF, Pantanowitz L, Rossi ED. Routine Digital Pathology Workflow: The Catania Experience. J Pathol Inform 2017;8:51.

7 L'Imperio V, Brambilla V, Cazzaniga G, Ferrario F, Nebuloni M, Pagni F. Digital pathology for the routine diagnosis of renal diseases: a standard model. J Nephrol 2021;34:681-668.

8 Evans AJ, Brown RW, Bui MM, et al. Validating Whole Slide Imaging Systems for Diagnostic Purposes in Pathology . Arch Pathol Lab Med 2022;146:440-450. https://doi.org/10.5858/arpa.2020-0723-cp

9 Thorstenson S, Molin J, Lundström C. Implementation of large-scale routine diagnostics using whole slide imaging in Sweden: Digital pathology experiences 2006-2013. J Pathol Inform 2014;5:14.

10 Eloy C, Vale J, Curado M, et al. Digital Pathology Workflow Implementation at IPATIMUP. Diagnostics (Basel) 2021;11. https://doi.org/10.3390/diagnostics11112111

11 Montezuma D, Monteiro A, Fraga J, et al. Digital Pathology Implementation in Private Practice: Specific Challenges and Opportunities . Diagnostics 2022;12:529. https://doi.org/10.3390/diagnostics12020529

12 Griffin J, Treanor D. Digital pathology in clinical use: where are we now and what is holding us back? Histopathology 2017;70:134-45.

13 Dawson H. Digital pathology - Rising to the challenge. Front Med 2022;9:888896.

14 Fraggetta F, L'Imperio V, Ameisen D, et al. Best Practice Recommendations for the Implementation of a Digital Pathology Workflow in the Anatomic Pathology Laboratory by the European Society of Digital and Integrative Pathology (ESDIP). Diagnostics (Basel) 2021;11. https://doi.org/10.3390/diagnostics11112167

15 Petrides AK, Bixho I, Goonan EM, et al. The Benefits and Challenges of an Interfaced Electronic Health Record and Laboratory Information System: Effects on Laboratory Processes. Arch Pathol Lab Med 2017;141:410-417.

16 Rampy BA, Glassy EF. Pathology Gross Photography: The Beginning of Digital Pathology. Clin Lab Med 2016;36:67-87.

17 Kang HP, Joseph Sirintrapun S, Nestler RJ, Parwani AV. Experience With Voice Recognition in Surgical Pathology at a Large Academic Multi-Institutional Center. Am J Clin Pathol 2010;133:156-159. https://doi.org/10.1309/ajcpoi5f1lpslzkp

18 Patel A, Balis UGJ, Cheng J, et al. Contemporary Whole Slide Imaging Devices and Their Applications within the Modern Pathology Department: A Selected Hardware Review. J Pathol Inform 2021;12:50.

19 Banks P, Brown R, Laslowski A, et al. A Proposed Set of Metrics to Reduce Patient Safety Risk From Within the Anatomic Pathology Laboratory. Lab Med 2017;48:195-201.

20 Stathonikos N, Nguyen TQ, van Diest PJ. Rocky road to digital diagnostics: implementation issues and exhilarating experiences. J Clin Pathol 2021;74:415-420.

21 Borowsky AD, Glassy EF, Wallace WD, et al. Digital Whole Slide Imaging Compared With Light Microscopy for Primary Diagnosis in Surgical Pathology. Arch Pathol Lab Med 2020;144:1245-1253.

22 Mukhopadhyay S, Feldman MD, Abels E, et al. Whole Slide Imaging Versus Microscopy for Primary Diagnosis in Surgical Pathology: A Multicenter Blinded Randomized Noninferiority Study of 1992 Cases (Pivotal Study). Am J Surg Pathol 2018;42:39-52.

23 Mills AM, Gradecki SE, Horton BJ, et al. Diagnostic Efficiency in Digital Pathology . Am J Surg Pathol 2018;42:53-59. https://doi.org/10.1097/pas.0000000000000930

24 Ghosh A, Brown GT, Fontelo P. Telepathology at the Armed Forces Institute of Pathology: A Retrospective Review of Consultations From 1996 to 1997. Arch Pathol Lab Med 2018;142:248-252.

25 Caputo A, D'Antonio A. Digital pathology: the future is now. Indian J Pathol Microbiol 2021;64:6-7.

26 Hanna MG, Pantanowitz L. Why is digital pathology in cytopathology lagging behind surgical pathology? Cancer Cytopathol 2017;125:519-520.

27 Girolami I, Pantanowitz L, Marletta S, et al. Diagnostic concordance between whole slide imaging and conventional light microscopy in cytopathology: A systematic review. Cancer Cytopathol 2020;128:17-28.

28 Eccher A, Girolami I. Current state of whole slide imaging use in cytopathology: Pros and pitfalls. Cytopathology 2020;31:372-378.

29 Antonini P, Santonicco N, Pantanowitz L, et al. Relevance of the College of American Pathologists guideline for validating whole slide imaging for diagnostic purposes to cytopathology. Cytopathology 2023;34:5-14 https://doi.org/10.1111/cyt.13178

30 Caputo A, Pepe L, Fraggetta F. Current State of Cytologic-Histologic Correlation Implementation for North American and International Laboratories. Arch. Pathol. Lab. Med 2023;147:15-16.

31 Caputo A, Macrì L, Gibilisco F, et al. Validation of full-remote reporting for cervicovaginal cytology. The Caltagirone-Acireale distributed lab. J Am Soc Cytopathol 2023; in press. DOI: https://doi.org/10.1016/j.jasc.2023.06.001

32 Caputo A, D'Ardia A, Sabbatino F, et al. Testing EGFR with Idylla on Cytological Specimens of Lung Cancer: A Review. Int J Mol Sci 2021;22. https://doi.org/10.3390/ijms22094852

33 Ghosh A, Brown GT, Fontelo P. Telepathology at the Armed Forces Institute of Pathology: A Retrospective Review of Consultations From 1996 to 1997. Arch Pathol Lab Med 2018;142:248-252.

34 Pagni F, Bono F, Di Bella C, Faravelli A, Cappellini A. Virtual surgical pathology in underdeveloped countries: The Zambia Project. Arch Pathol Lab Med 2011;135:215-259.

35 Nguyen LN, Crothers BA, Davey DD, et al. Current State of Cytologic-Histologic Correlation Implementation for North American and International Laboratories. Arch Pathol Lab Med 2023;147:52-61 https://doi.org/10.5858/arpa.2021-0223-CP

36 Zarbo RJ. The Unsafe Archaic Processes of Tissue Pathology. Am J Clin. Pathol 2022;158:4-7.

37 Fulawka L, Blaszczyk J, Tabakov M, Halon A. Assessment of Ki-67 proliferation index with deep learning in DCIS (ductal carcinoma in situ). Sci Rep 2022;12:3166.

38 Wang X, Wang L, Bu H, et al. How can artificial intelligence models assist PD-L1 expression scoring in breast cancer: results of multi-institutional ring studies . npj Breast Cancer 2021;7(1). https://doi.org/10.1038/s41523-021-00268-y

39 Caputo A, D'Antonio A, Memoli D, et al. Ki67 in Gleason Pattern 3 as a Marker of the Presence of Higher-Grade Prostate Cancer. Appl Immunohistochem Mol Morphol 2021;29:112-7.

40 Marini N, Marchesin S, Otálora S, et al. Unleashing the potential of digital pathology data by training computer-aided diagnosis models without human annotations. NPJ Digit Med 2022;5:102.

41 Raciti P, Sue J, Retamero JA, et al. Clinical Validation of Artificial Intelligence--Augmented Pathology Diagnosis Demonstrates Significant Gains in Diagnostic Accuracy in Prostate Cancer Detection. Arch Pathol Lab Med 2022. https://doi.org/10.5858/arpa.2022-0066-OA

42 Sanghvi AB, Allen EZ, Callenberg KM, Pantanowitz L. Performance of an artificial intelligence algorithm for reporting urine cytopathology. Cancer Cytopathol 2019;127:658-666.

[43] Pantanowitz L, Bui MM, Chauhan C, et al. Rules of engagement: Promoting academic-industry partnership in the era of digital pathology and artificial intelligence. Acad Pathol 2022;9:100026.

[44] Moulin P, Grünberg K, Barale-Thomas E, van der Laak J. IMI-Bigpicture: A Central Repository for Digital Pathology. Toxicol Pathol 2021;49:711-713.

[45] Browning L, Colling R, Rakha E, et al. Digital pathology and artificial intelligence will be key to supporting clinical and academic cellular pathology through COVID-19 and future crises: the PathLAKE consortium perspective . J Clin Pathol 2021;74:443-447. https://doi.org/10.1136/jclinpath-2020-206854

[46] Lancellotti C, Cancian P, Savevski V, et al. Artificial Intelligence & Tissue Biomarkers: Advantages, Risks and Perspectives for Pathology. Cells 2021;10. https://doi.org/10.3390/cells10040787

[47] Gupta R, Kurc T, Sharma A, Almeida JS, Saltz J. The Emergence of Pathomics . Current Pathobiology Report. 2019;7:73-84. https://doi.org/10.1007/s40139-019-00200-x

[48] Osareh A, Shadgar B. Machine learning techniques to diagnose breast cancer. In: 2010 5th International Symposium on Health Informatics and Bioinformatics. 2010, p. 114-20.

[49] Bera K, Schalper KA, Rimm DL, Velcheti V, Madabhushi A. Artificial intelligence in digital pathology - new tools for diagnosis and precision oncology. Nat Rev Clin Oncol 2019;16:703-715.

[50] Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature 2017;542:115-118.

[51] Marletta S, Pantanowitz L, Santonicco N, et al. Application of Digital Imaging and Artificial Intelligence to Pathology of the Placenta. Pediatr Dev Pathol 2022;10935266221137953.

[52] Majidova K, Handfield J, Kafi K, Martin RD, Kubinski R. Role of Digital Health and Artificial Intelligence in Inflammatory Bowel Disease: A Scoping Review. Genes 2021;12. https://doi.org/10.3390/genes12101465

[53] Lee JJ, Jedrych J, Pantanowitz L, et al. Validation of Digital Pathology for Primary Histopathological Diagnosis of Routine, Inflammatory Dermatopathology Cases. Am J Dermatopathol 2018;40:17-23.

[54] Yuan Y. Modelling the spatial heterogeneity and molecular correlates of lymphocytic infiltration in triple-negative breast cancer. J R Soc Interface 2015;12. https://doi.org/10.1098/rsif.2014.1153

[55] Corredor G, Wang X, Zhou Y, et al. Spatial Architecture and Arrangement of Tumor-Infiltrating Lymphocytes for Predicting Likelihood of Recurrence in Early-Stage Non-Small Cell Lung Cancer. Clin Cancer Res 2019;25:1526-1534.

[56] Saltz J, Gupta R, Hou L, et al. Spatial Organization and Molecular Correlation of Tumor-Infiltrating Lymphocytes Using Deep Learning on Pathology Images. Cell Rep 2018;23:181-93.e7.

[57] Lu C, Romo-Bucheli D, Wang X, et al. Nuclear shape and orientation features from H&E images predict survival in early-stage estrogen receptor-positive breast cancers. Lab Invest 2018;98:1438-1448.

[58] Kapil A, Meier A, Zuraw A, et al. Deep Semi Supervised Generative Learning for Automated Tumor Proportion Scoring on NSCLC Tissue Needle Biopsies. Sci Rep 2018;8:17343.

[59] Kather JN, Pearson AT, Halama N, et al. Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer. Nat Med 2019;25:1054-6.

[60] Beretta C, Ceola S, Pagni F, et al. The role of digital and integrative pathology for the detection of translocations: a narrative review . Precision Cancer Medicine 2022;5:16-16. https://doi.org/10.21037/pcm-21-56

[61] Langer M, Oster D, Speith T, et al. What do we want from Explainable Artificial Intelligence (XAI)? - A stakeholder perspective on XAI and a conceptual model guiding interdisciplinary XAI research . Artificial Intelligence 2021;296:103473. https://doi.org/10.1016/j.artint.2021.103473

[62] Combi C, Amico B, Bellazzi R, et al. A manifesto on explainability for artificial intelligence in medicine. Artif Intell Med 2022;133:102423.

[63] Lazard T, Bataillon G, Naylor P, et al. Deep learning identifies morphological patterns of homologous recombination deficiency in luminal breast cancers from whole slide images. Cell Rep Med 2022;3:100872.

[64] Fremond S, Andani S, Barkey Wolf J, et al. Interpretable deep learning model to predict the molecular classification of endometrial cancer from haematoxylin and eosin-stained whole-slide images: a combined analysis of the PORTEC randomised trials and clinical cohorts. Lancet Digit Health 2022; https://doi.org/10.1016/S2589-7500(22)00210-2

[65] Chauhan C, Gullapalli RR. Ethics of AI in Pathology: Current Paradigms and Emerging Issues. Am J Pathol 2021;191:1673-1683.

[66] Larson EJ. The Myth of Artificial Intelligence. 2021. https://doi.org/10.4159/9780674259935

[67] Mitchell M. Artificial Intelligence: A Guide for Thinking Humans. Penguin UK 2019.

[68] Berbís MA, Alvaro Berbís M, McClintock DS, et al. Computational pathology in 2030: a Delphi study forecasting the role of AI in pathology within the next decade . eBioMedicine 2023;88:104427. https://doi.org/10.1016/j.ebiom.2022.104427

[69] Di Giacomo D, Ranieri J, D'Amico M, Guerra F, Passafiume D. Psychological Barriers to Digital Living in Older Adults: Computer Anxiety as Predictive Mechanism for Technophobia. Behav Sci 2019;9. https://doi.org/10.3390/bs9090096

[70] Roy SF, Cecchini MJ. Implementing a structured digital-based online pathology curriculum for trainees at the time of COVID-19. J Clin Pathol 2020;73:444.

[71] Mea VD, Carbone A, Di Loreto C, et al. Teaching Digital Pathology: The International School of Digital Pathology and Proposed Syllabus. J Pathol Inform 2017;8:27.

[72] Zaresani A, Scott A. Does digital health technology improve physicians' job satisfaction and work-life balance? A cross-sectional national survey and regression analysis using an …. BMJ Open 2020 https://bmjopen.bmj.com/content/10/12/e041690.abstract

[73] Schubert M. Leading by Example . The Pathologist. 2019 [cited 2023 Jan 5]; https://thepathologist.com/inside-the-lab/leading-by-example

[74] Williams BJ, Bottoms D, Clark D, Treanor D. Future-proofing pathology part 2: building a business case for digital pathology . Journal of Clinical Pathology 2019;72:198-205. https://doi.org/10.1136/jclinpa