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# The evolving landscape of anatomic pathology

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ABSTRACT

Anatomic pathology has changed dramatically in recent years. Although the microscopic assessment of tissues and cells is and will remain the mainstay of cancer diagnosis molecular profiling has become equally relevant. Thus, to stay abreast of the evolving landscape of today's anatomic pathology, modern pathologists must be able to master the intricate world of predictive molecular pathology. To this aim, pathologists have had to acquire additional knowledge to bridge the gap between clinicians and molecular biologists. This new role is particularly important, as cases are now collegially discussed in molecular tumor boards (MTBs). Moreover, as opposed to traditional pathologists, modern pathologists have also adamantly embraced innovation while keeping a constant eye on tradition. In this article, we depict the highlights and shadows of the upcoming "Anatomic Pathology 2.0" by placing particular emphasis on the pathologist's growing role in the management of cancer patients.

## 1. Introduction

Conventional diagnostic microscopy, which relies on the identification of structural alterations and their effects on cellular and tissue function (Funkhouser, 2018), will not be replaced any time soon by any other form of diagnostic testing, primarily because of its undisputable ease of use, affordability, and accuracy. As the late Professor Juan Rosai stated in his work *Why Microscopy will remain a cornerstone of surgical pathology* [2007] "There is no other technique that provides abundant, quick and cost-effective information as the "classical" microscopy. so that is still probably true that morphologic analysis by skilled observers. will be with us for many years to come" (Rosai, 2007). However, because of the advent of precision medicine, along with the expanding array of advanced technologies, pathology is bound to change dramatically. The reason is that the last decades have seen a remarkable increase in the development of different ancillary techniques able to provide actionable information in addition to that provided by histopathological analyses. This (r)evolution has entailed a progressive adaptation to new clinical challenges, placing pathologists at the forefront of the era of precision medicine. Indeed, with the introduction of different molecular tools (e.g., next-generation sequencing, NGS) to investigate the underlying biological mechanisms of cancer development, molecular pathologists have now gained a pivotal role in the therapeutic decision-making process by facilitating the translation of biomarker discoveries to clinical application (Angerilli et al., 2021). Such transition has been painstakingly accomplished through the optimization of available biological material to obtain both diagnostic and predictive information— a process that is significantly changing today's routine histo/cytopathology practice. Moreover, the gradual implementation of digitalization, including computer aided diagnosis (CAD), has helped to simplify and to

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empower the laboratory workflow (Parwani, 2019). Indeed, digitization has drastically reduced costs and turnaround time, as well as improved remote assessment of samples for primary diagnosis or consultation (Parwani, 2019). These innovations, along with the possibility of sharing experiences, knowledge, and information through the recently "colonized" social media, represent the basis for a parallel "digital revolution". This review discusses these innovative and integrative roles from a *young pathologist's* perspective by unveiling the highlights and shadows of the upcoming Anatomic Pathology 2.0.

## 2. Modern cytopathology: the revival of an ancient technique

Cytopathology is a well-established diagnostic approach owing to its low cost, reliability, and minimal invasiveness compared with other methodologies. In recent years, several efforts have been made to standardize and optimize the classification systems in cytopathology to facilitate communication between cytopathologists and other physicians (Pitman and Black-Schaffer, 2017). The titanic endeavour to share clinically relevant information has resulted in the development of novel classification systems, including thyroid (Cibas and Ali, 2017; Baloch and LiVolsi, 2020), salivary glands (Rossi et al., 2017a; Rossi, 2021), breast (Field et al., 2019), endometrial (Fulciniti et al., 2018), urinary (Barkan et al., 2016), pancreatic-biliary (Layfield, 2021; Pitman et al., 2014; Sung et al., 2020), serous fluids (Pinto et al., 2021; Chandra et al., 2019) and cervical (Nayar and Wilbur, 2017) cytopathology. These classification systems are highly critical not only to standardize diagnostic terms in cytopathological reports but also to define the risk of malignancy (ROM) for each morphological category (Lindley et al., 2014).

Essentially, one of the main differences between conventional surgical pathologists and interventional cytopathologists is that whereas the former performs cytopathological examination on specimens sampled by other physicians, the latter triage the aspirated material by themselves. Such practice has been made possible thanks to the acquisition of professional expertise in fine needle aspiration (FNA) procedures under ultrasound (US)-guidance (Bellevicine et al., 2016). An essential component of US-FNA is the rapid on-site evaluation (ROSE) technique. Indeed, this auxiliary technique enables modern cytopathologists to directly assess the adequacy of the aspirated material, thereby significantly reducing inadequate results (Bellevicine et al., 2016). Moreover, it allows them to plan further FNA steps to enrich the sampled material for ancillary procedures, including molecular analysis (De Luca et al., 2020). Of note, ROSE can also be performed by a dedicated cytotechnician when endoscopic or computed tomography (CT)-guided FNAs are performed by other specialists (Jain et al., 2018; Gregg et al., 2019; Righi et al., 2017).

Another major difference between conventional histology and interventional cytopathology is that the latter can successfully exploit scant cytological samples to evaluate druggable biomarkers when histological samples are either insufficient or unattainable. The clinical efficacy of cytological analyses, especially in advanced cancers has been recognized as a valid alternative to tissue biopsies by the major lung cancer associations. For example, the guidelines from the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) now recommend the use of cytological samples for molecular analysis in advanced stage non-small cell lung cancer (NSCLC) patients (Lindeman et al., 2013, 2018). Thus, in this rapidly evolving setting, molecular cytopathologists have gained a central role in bridging the gap between traditional microscopy and novel molecular approaches (Salto-Tellez, 2018). Indeed, in addition to performing morphological analyses and molecular profiling of cytological specimens, molecular cytopathologists are also responsible for assessing the adequacy of cytological material either retrieved from the archives or shipped by external institutions for molecular analysis (Bussolati et al., 2015; Pisapia et al., 2021a, 2021a). Finally, a major advantage of molecular cytopathology is that after a first microscopic assessment, molecular cytopathologists can directly request a biomarker evaluation as a "reflex test", thereby reducing turnaround times and accelerating initiation of treatment (Fassan, 2018). Altogether, we conclude that the revival of molecular cytopathology in today's clinical practice stems from the need to tackle some of the many challenges posed by precision medicine. Indeed, we have highlighted the many reasons why molecular cytopathologists play a critical role in modern multidisciplinary team (MDT) meetings by providing timely and accurate diagnoses, as well as support for the overall clinical decision-making process.

## 3. Modern histopathology: much more than morphology-based diagnosis

Since the time of Marcello Malpighi, the founder of microscopic anatomy in the 17th century, pathologists have used the microscope for diagnostic purposes, gradually progressing from macroscopic/autopsy observations to microscopic/ultrastructural observations (van den Tweel and Taylor, 2010). Remarkably, since its inception in the 1600 s up to our days, the optical microscope has remained the most widely used diagnostic tool for histological examination worldwide. Tissues are generally visualized with haematoxylin and eosin (H&E) staining agents. Thus, for decades, pathologists have visualized cellular morphological structures of tissues in "pink and purple". Ample descriptions of anatomical-pathological pictures have been characterized and defined on the basis of this technique and its artifacts. However, in today's era of technological revolution, the field of anatomic pathology is bound to change once again, progressing from morphology-based diagnosis to molecular-based diagnosis. In this rapidly evolving scenario, the development of new machinery and methodologies is placing histopathology at risk of becoming obsolete in diagnostic pathology. This risk of this foreseeable, yet rather unlikely future, can be better rendered by one of Bernard of Chartres' beautiful analogies stating that "*We are like dwarfs on the shoulders of giants*". Applied to today' s evolving landscape of anatomic pathology, this would mean that pathologists must bear in mind that the task of modern pathology is not to replace histopathology but to make continual improvements in the discipline by building upon the foundations of our predecessors. As of today, H&E on formalin-fixed paraffin embedded (FFPE) tissues still represent a cornerstone of the diagnostic process, and H&E staining remains a fundamental tool for identifying prognostic factors that are routinely integrated in pathology reports (e.g., histological grades and the presence of lymph-vascular invasion).

In addition to the diagnostic and prognostic role of histopathology, pathologists must acknowledge the fundamental importance of confirming the adequacy of samples for molecular analysis to obtain robust and reliable results. In this setting, the pathologist plays a primary role in selecting adequate material for the construction of clinical biobanks and in executing mutational and genomic analyses.

Finally, pathologists should also bear in mind that the key to achieving optimal molecular and prognostic characterization lies in careful and precise histological preparation. For this reason, we adamantly support the notion that Pathological Anatomy 2.0 must base its activities on innovative techniques and tools while always paying homage to its morphological origins.

## 4. Molecular and predictive pathology: connecting morphology and biology for patients' management

The Food and Drug Administration (FDA) approval of novel therapeutic agents based on tumor-agnostic biomarkers has paved the way toward the modern era of translational molecular pathology. Recently approved drugs include pembrolizumab for the treament of microsatellite instability-high (MSI-H)/ mismatch repair deficient (dMMR) solid tumors and larotrectinib and entrectinib for the treatment of neurotrophin receptor tyrosine kinase (*NTRK*) fusion-positive tumors

(Seligson et al., 2021). Several technologies are now available for biomarker profiling, including immunohistochemistry (IHC), polymerase chain reaction (PCR)-based techniques, and NGS (Pagni et al., 2019). Unsurprisingly, in the highly complex scenario of precision medicine, the increasing demand for biomarker testing, alongside with the need to optimize the available tissue material, has spurred a terrific revolution in predictive molecular laboratories. Noteworthy, to avoid leaving any cancer patient behind, molecular predictive laboratories have shifted from single gene testing approaches (e.g., RT-PCR) to more innovative multiplexed high-throughput platforms (e.g., NGS). A striking feature of these sequencing platforms is that they can simultaneously analyse several hotspot clinically relevant gene alterations in different patients even when dealing with very low nucleic acid inputs.

In this fast-changing landscape of cancer testing and the increasing demands of predictive, preventing, and personalized medicine, modern pathologists should, therefore, be aware of the importance of these new molecular platforms to streamline the whole process of patients' management and, thus, strongly advocate their application in routine clinical practice. Remarkably, the user-friendly workflow and the lower costs of NGS platforms compared to more traditional ones render their adoption in clinical practice highly feasible and sustainable, as recently demonstrated by an Italian multicenter study, namely the KWAY project (Pisapia et al., 2022). Indeed, this study highlights two major strengths: the first is that these platforms drastically shorten the hands-on time required for molecular testing activities, thereby reducing the turnaround time; the second is that they also reduce the overall costs of testing per cancer patient. From a patient's perspective, the adoption of NGS offers them the opportunity to receive faster diagnoses, faster initiation of targeted treatments, and prolonged survival. Thus, keeping pace with this rapid evolution is daunting but possible so long as multidisciplinary groups are created to address the multiple challenges. These groups should include technicians, molecular biologists, and bioinformaticians specialized in molecular diagnostics, along with pathologists able to select the most appropriate samples and to integrate clinicopathological and molecular information in pathology reports (Angerilli et al., 2021).

Adding to the complexity of modern pathology is the fast growing number of tumor-specific biomarkers, testing methods, and interpretation guidelines. For instance, the International Immuno-Oncology Biomarker Working Group (a panel of pathologists and expert scientists) has licensed the first international guidelines on tumor-infiltrating lymphocyte (TIL) assessment in breast cancer (Salgado et al., 2015) and solid tumors (Dieci et al., 2018; Hendry et al., 2017). It is worth noting that the lack of clear-cut thresholds and widely adopted guidelines for key immune-related biomarkers, e.g., tumor mutational burden (TMB), is yet evident. For instance, owing to the rationale that a higher load of mutations leads to increased neoantigen production and immunogenicity, TMB is often considered a surrogate marker for neoantigen load (Gjoerup et al., 2020). However, a recent study urged strong caution in using TMB as a predictive biomarker for immune checkpoint blockade (ICB) therapy in a pan-cancer pattern across all solid tumours. In particular, the study points out that since predictive cut-off values tend to vary according to the histological types, it is highly unlikely that a single tissue-agnostic definition of high TMB could serve as a useful predictor of ICI response (McGrail et al., 2021).

Regarding the clinical implementation of the ever-increasing number of new predictive biomarkers, pathologists ought to be updated on the latest assessment strategies (Angerilli et al., 2021). For example, for the evaluation of programmed death-ligand 1 (PD-L1), one of the major ICB biomarkers, various staining platforms, antibody clones (e.g., 22C3, SP142), scoring systems (e.g., immune cells, combined positive score), and cut-off values have been proposed. Despite all these variables, imperative harmonization efforts are still ongoing to standardize pre-analytical and interpretative phases of PD-L1 testing (e.g., NSCLC) (Sajjadi et al., 2020). Hence such biomarkers require considerable expertise and specific training since interpretation guidelines are often incompatible across various tumour types (Hofman, 2017). Hence, to optimize precision medicine, some authors warrant further stratification of patients into clinically meaningful subgroups through translational tools. In this scenario, pathologists can take further steps to develop, validate, and implement such biomarkers in clinical practice (Walk et al., 2020).

**Table 1**
Overview on the principal molecular techniques with advantages and disadvantages.

| Methodology | Advantages | Disadvantages |
|---|---|---|
| Direct Sequencing (Sec. Sanger) | - "gold standard" molecular approach<br>- ability to identify known and unknown genomic alterations<br>- high specificity | - low sensitivity<br>- limited multiplexing power |
| RT-PCR | - low TAT<br>- high sensitivity<br>- cheap | - ability to identify only known and well characterized genomic alterations<br>- limited multiplexing power. |
| dPCR | - low TAT<br>- cheap<br>- high sensitivity (higher than RT-PCR) | - ability to identify only known and well characterized genomic alterations<br>- limited multiplexing power |
| NGS | - high sensitivity<br>- ability to identify known and unknown genomic alterations<br>- high multiplexing power. | - careful validation is required;<br>- bioinformatics support is needed;<br>- skilled laboratory staff is required. |

Abbreviations: dPCR: digital polymerase chain reaction; NGS: next generation sequencing; RT-PCR: real time polymerase chain reaction; TAT: turnaround time.

Table 1 summarizes the advantages and disadvantages of today's principal molecular techniques.

## 5. Digital pathology and artificial intelligence: automation to simplify the workflow

The introduction of digital pathology and artificial intelligence (AI) in clinical laboratories represents another major paradigm shift in anatomic pathology. Briefly, the term digital pathology is often inappropriately restricted to the employment of glass slide scanners used to obtain whole-slide images (WSIs) for sharing purposes. However, the whole gamut of this broad field runs from the complete automation of the entire anatomic pathology workflow to the application of digitized slides for primary diagnosis and consultation purposes. Moreover, digital pathology has recently been integrated with image analysis and artificial intelligence (AI) tools, which further streamline the overall laboratory work of clinical pathologists (Niazi et al., 2019). Unfortunately, although the FDA has recently approved some of the available WSI devices for primary diagnoses (Evans et al., 2018), only few pathology departments worldwide have actually undergone a complete digital transition (Thorstenson et al., 2014). One major obstacle to its full application is a substantial lack of guidance on how to fully bring about this paradigm shift. A case in point is that the existing guidelines are centred primarily on the validation of the WSI alone (Griffin and Treanor, 2017; Evans et al., 2021). Interestingly, some consolidated Italian experiences have recently demonstrated that this setback could be overcome by introducing several types of software, namely, adequate tracking systems based on the employment of 2D-barcodes (Hanna and Pantanowitz, 2015) and fully integrated laboratory information systems (LIS); other studies have instead suggested the application of different check-points during the sample processing phases for quality control (QC) purposes (Fraggetta et al., 2021; Rossi et al., 2017b; L'Imperio et al., 2020a).

Clearly, all these modifications would require the optimization of the precious, yet scarce biological material for cancer characterization. In

**Table 2**
Some of the principal commercially available platforms to obtain WSIs and relative technical features.

| Manufacturer | Model | Imaging mode (s) | Slide capacity | Scan speed * | Image capture magnification | Image capture resolution** | Digital slide format | Multilayer support | Barcode support | Special features |
|---|---|---|---|---|---|---|---|---|---|---|
| **Leica** | Aperio GT 450 DX | Brightfield | 450 (15 racks of 30 slides) | 40x: 32 s | 40x | 40x: 0.26 | SVS, TIFF | – | 1D, 2D | Continuous loading; automatic image control |
| **Philips** | IntelliSite Ultra-Fast Scanner | Brightfield | 300 slides (15 racks of 20 slides) | 40x: 60 s | 40x | 40x: 0.25 | RAW, iSyntax | – | 1D, 2D | FDA approved |
| **3DHistech** | Pannoramic 1000 DX | Brightfield | 1000 slides | 40x: 32 s | 20x - 40x | 40x: 0.24 | DICOM, MRXS | Optional multilayer (Z-stack) and extended focus scanning | 1D, 2D | Continuous loading; flexibility (arbitrary scanning) |
| **Hamamatsu** | NanoZoomer S360 | Brightfield | 360 slides | 40x: 30 s | 20x - 40x | 20x: 0.46<br>40x: 0.23 | JPEG | Z-stack available | 1D (standard feature), 2D (option) | Automatic image confirmation |
| **Olympus** | VS200 | Brightfield, Darkfield, Phase Contrast (optional), Simple Polarization (optional), Fluorescence (optional) | 210 slides max (up to 35 trays) | 20x: 80 s | 2x, 4x, 10x, 20x, 40x, 60x, and 100x | 10x: 0.548<br>20x: 0.274<br>40x: 0.137<br>60x: 0.091<br>100x: 0.055 | vsi, JPEG, and TIFF | Z stack imaging, extended focus imaging (EFI) | 1D, 2D | – |
| **Ventana** | DP 200 | Brightfield | 6 single slides, 3 double slides | 20x: 36 s<br>40x: 73 s | 20x - 40x | 20x: 0.465<br>40x: 0.23 | DICOM, Ventana. bif | Z-stack available | 1D, 2D | EU CE-marked IVD |

Abbreviations: 1D, one dimensional; 2D, two dimensional; WSI, whole slide imaging
* The listed scanning speeds are for 15 mm × 15 mm area (bright field).
** The listed resolutions are in microns/pixel.

this setting, one of the most immediate applications of WSI might be the digitization of cytological smears destined for molecular analysis. Creating databases of scanned cyto/histological samples could serve multiple purposes. For example, they could give rise to virtual repositories for possible medico-legal issues (Caputo et al., 2021) or could represent an invaluable educational resource for university departments and residency programs (Boyce, 2015; Cheng et al., 2016). This would enable students and residents to have direct access to the cases of interest during multidisciplinary meetings and molecular tumour boards (Nofech-Mozes and Jorden, 2014). Finally, such databases would also allow remote access and off-site work under certain critical circumstances, as the recent coronavirus 19 (COVID-19) pandemic (Hassell et al., 2021).

In addition to the significant impact that a digital transition would have on the routine clinical practice and on the overall job of molecular pathologists, the application of AI would also offer the unmissable opportunity to manage the enormous amount of data generated by every pathology department through specific algorithms. Remarkably, simple image analysis instruments, as well as complex machine learning algorithms, are already being currently employed in everyday clinical practice for the most disparate purposes, including the differentiation between benign and malignant lesions (Cai, 2018), the prognostic evaluation of specific histological features (Veta et al., 2012), and the detection of cytological alterations that can predict drug response (Wang et al., 2018). In the setting of predictive pathology, the application of different types of easy-to-access image analysis software (e.g., Fiji, ImageJ) has already shown to be useful in enabling precise evaluation of immunohistochemistry bio-selectors. Indeed, studies have demonstrated how these types of software can properly quantify PD-L1 tumour proportion score (TPS) in NSCLC thereby helping clinicians to differentiate subsets of patients who might benefit from first-line immunotherapy and to identify those harbouring specific gene alterations (Beretta et al., 2022). Moreover, the possibility of selecting the material for molecular analysis in a single-cell fashion through integrated WSI and laser capture microdissection (LCD) can further facilitate the predictive characterization of these neoplasms, especially in cases characterized by a low tumour fraction for the presence of abundant inflammatory background or necrosis (Coope et al., 2021). From all these preliminary inputs, it is clear that the introduction of different types of digital pathology software, as well as AI, in routine clinical practice can drastically simplify the work of molecular pathologists and achieve sustainable and precision oncology/pathology systems.

Table 2 summarizes some of the principal commercially available platforms for WSIs.

## 6. The importance of establishing high-quality social media

In recent years, the professional use of social media has gained increasing popularity among molecular pathologists. Although some pathologists are still reticent (Gardner and Allen, 2019), there are currently more than 5000 users and pathology-related accounts on Twitter (Gardner and McKee, 2019), and the list of available platforms for this purpose is further expanding along with the most post popular websites (e.g. Facebook, Instagram, and LinkedIn). The strong appeal of the so-called #PathTwitter community most likely hinges on the intuitive and easy-to-access nature of the social network that gives pathologists the opportunity to share interesting educational cases by opening constructive discussions on topics of particular interest. Not surprisingly, the use of these platforms is increasingly acquiring a more didactic nature thanks to the creation of brief summaries on specific arguments (e.g., #PathTweetorials), the implementation of web-based journal clubs (e.g., #dermpathJC (Gottesman et al., 2018)), and the streaming

**Table 3**
Some of the national and international pathology societies and organizations with available accounts on Facebook and Twitter.

| Organization | Facebook Page (preceded by www.facebook.com) | Twitter Handle |
|---|---|---|
| United States and Canadian Academy of Pathology (USCAP) | /TheUSCAP/ | @TheUSCAP |
| College of American Pathologists | /capathologists/ | @pathologists |
| American Board of Pathology | /ABPathology/ | @TheABPath |
| American Pathology Foundation | /PATHconnect/ | @PATHConnect |
| American Registry of Pathology/ARP Press/ AFIP fascicles | /American-Registry-of-PathologyARP-PressAFIP-Fascicles-290677394597616/ | @ARP_Press |
| American Society for Clinical Pathology | /ASCP.Chicago/ | @ASCP_Chicago |
| American Society of Cytopathology | /cytopathology/ | @cytopathology |
| American Society of Dermatopathology | /ASDermPath/ | @ASDPTweets |
| Association for Molecular Pathology | /AMPathology/ | @AMPath |
| Association for Pathology Informatics | /pathbytes/ | @apipathbytes |
| Canadian Association of Pathologists | /canadian.association.pathologists/ | @CAPACP |
| International Society of Dermatopathology | /IntSocDermpath/ | @IntSocDermpath |
| Papanicolaou Society of Cytopathology | /PapanicolaouSociety/ | @PapSociety |
| Sociedad Española de Anatomía Patológica - División Española de la International Academy of Pathology (SEAP-IAP) | /SEAP.IAP/ | @SEAP_IAP |
| Società Italiana di Anatomia Patologica e Citopatologia - Divisione Italiana de International Academy of Pathology (SIAPEC-IAP) | /SIAPEC/ | – |
| International Academy Cytology | /International-Academy-of-Cytology/187019668876100/ | @IACytology |
| British Division of the International Academy of Pathology | /newbdiap/ | @BritishDivIAP |
| European Society of Digital and Integrative Pathology (ESDIP) | /ESDIPatho/ | @ESDIPatho |
| European Society of Pathology (ESP) | /esp.pathology/ | @ESP_Pathology |
| International Society of Liquid Biopsy | – | @isliquidbiopsy |

of live conferences, all free of charge. This pathology network allows even the creation of large multi-institution research studies stemming from the original inputs (or Tweet) of users (Doxtader et al., 2019), thereby widening significant the scope of the interconnection between pathologists and researchers worldwide (Lepe et al., 2020). Moreover, the public engagement of patients' associations is another opportunity to share research data and improve knowledge. Social media has also revolutionized the editorial world, with the progressive recognition of surrogate scientific impact parameters (e.g., Altmetrics), which are increasingly being employed as measures of the real-time reach and impact of academic articles (Warren et al., 2017). This phenomenon has led some authors to propose these indices as complementary to the more widely employed citation metrics.

However, what makes these platforms unique is probably their interdisciplinary nature, which promotes continuous constructive debates among specialists from different disciplines (e.g., pathologists and oncologists). In particular, the rationale behind a recent Italian experience called "4oncommunity", developed by four of the co-authors of the present paper (MF, NF, FP and UM), was to share precious information among different professionals (technicians, biologists, medical doctors of different sub-specialities) in the setting of predictive molecular pathology in a complete agnostic way.

Remarkably, this initiative, which was first launched on a dedicated website (https://4oncommunity.com/) but and later directed to Twitter landing pages (@4oncommunity), is progressively acquiring popularity and has been found to be of great support in helping clinicians to manage complex oncologic scenarios. A similar approach, focused, though, on lung cancer, has been proposed on a Facebook professional platform, namely, "Workplace Lung Cancer". In detail, this platform, organized in different but interconnected "silos" hosting different specialists (e.g., pathologists, oncologists, radiologists, and pharmacists), provides the possibility of updating the community on the latest news by sharing experiences and by creating a network to assist clinicians in dealing with both easy and more complex issues in routine clinical practice.

Overall, considering all these advantages, our experiences, and the burgeoning literature on the application of social platforms in clinical practice, we adamantly support the use of social media in the field of molecular and predictive oncology to gain and share valuable insights into patient management.

Table 3 summarizes some of the most popular national and international pathology societies and organizations with available accounts on Facebook and Twitter.

## 7. The oncologist perspective on modern pathology / The strong oncologist-pathologist bond in modern pathology

The revolution that has taken place in the field of pathology over the last few decades has inevitably changed the way pathologists interact with other healthcare professionals and in particular with medical oncologists. Whereas in the era of traditional pathology, pathologists had a background role, consisting primarily of analysing tissues and communicating their histopathological findings to tumour boards, in the era of modern pathology, they have acquired a principal role in cancer diagnosis and treatment decision-making by working in tandem with oncologists. Several reasons may explain this phenomenon. One reason is the growing number of clinically relevant oncogenic drivers necessary for appropriate drug prescription. This phenomenon has sparked a series of challenges in terms of optimal management of tumour tissue and a high demand for novel sources to perform tumour genotyping, such as liquid biopsy (Russo et al., 2019a; Rolfo et al., 2021). Hence, in this highly demanding setting, a close collaboration between pathologists and medical oncologists has become instrumental in selecting optimal molecular tests, in maximizing test results, and, finally, in providing valuable information for treatment-decision making. A second reason for today's strong collaboration between oncologists and pathologists is the widespread implementation of NGS in routine clinical practice. Indeed, the huge body of information provided by NGS must be adequately interpreted by professionals before it can actually be used for clinical purposes. For instance, it must be filtered by appropriate tools for ranking and interpretation of genomic alterations, such as OncoKB and the European Society for Medical Oncology Scale for Clinical Actionability (ESCAT). Finally, it must be evaluated in the multidisciplinary context of molecular tumour boards (MTBs) (Leichsenring et al., 2019; Chakravarty et al., 2017; Russo et al., 2019b; Lee et al., 2019; Kato et al., 2020; Koopman et al., 2020; Pisapia et al., 2021b, 2021c).

Another important reason why oncologists largely rely on pathologists to make appropriate treatment decisions is the ample use of knowledge-based databases. These systems, as well, which collect and store real world data on molecular alterations and clinical outcomes, require high expertise in managing and interpreting the myriad of data they store. Given the clinical relevance of these databases, we recently embarked on a project consisting of an Italian multicentre study with the

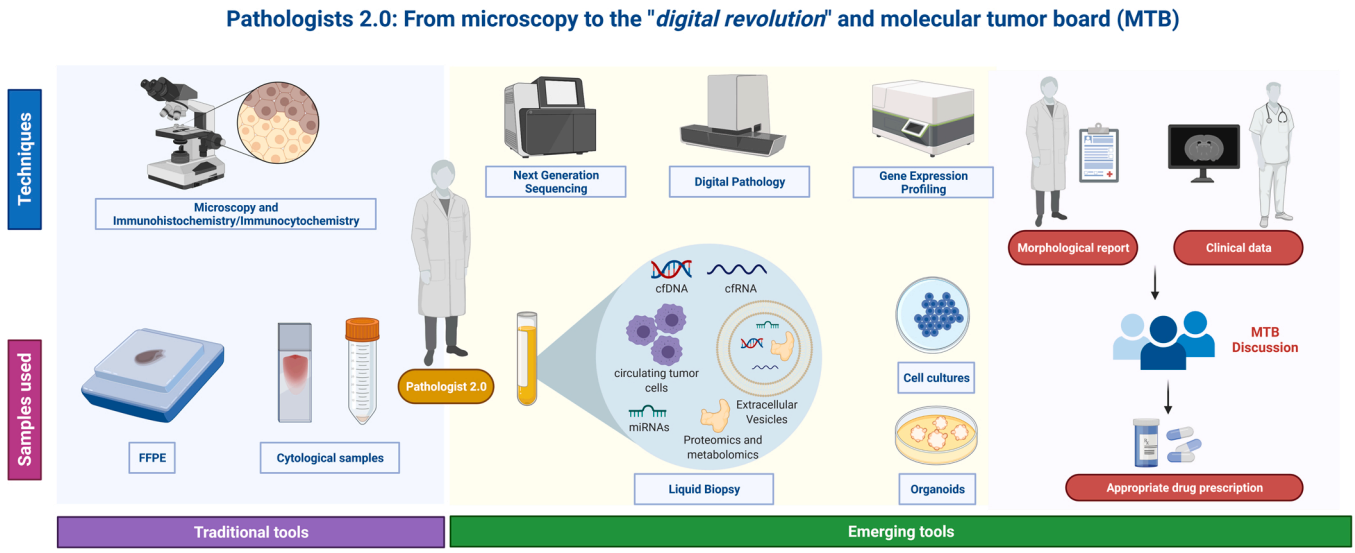


**Fig. 1.** Pathologists 2.0: from microscopy to the "digital revolution" and molecular tumour board (MTB). Beyond the traditional morphological evaluation of histo/cytological samples, modern pathologists have to cope with the rapid progress in the field of personalized medicine and cancer treatment. In particular, modern pathologists have to juggle in the intricate world of predictive molecular pathology and different molecular techniques and assays. In addition, besides tissue sampling, modern pathologists are also taking into account the application of novel sources of tumoral nucleic acids, including liquid biopsies. In this novel scenario, modern pathologists have acquired a crucial role in bridging the gap between clinicians and molecular technicians. Thus, they have now acquired a prominent role in modern MTB.

intent to produce an Italian knowledge database in which real-world data on *RAS* gene mutations in lung and colon cancers could be reported (Malapelle et al., 2021). We are currently still working on this project by considering not only *RAS* mutations but also other clinically relevant genomic alterations in advanced stage NSCLC (https://biomarkersatlas.com/).

Moreover, the pathologists' participation in MTB meetings also reflects the importance of their role in translating the latest scientific evidence into clinical practice by providing clinicians valuable information for tailored treatment plans.

Thus, it is becoming increasingly apparent that as the role of pathologists continues to evolve, so should the role of medical oncologists. Indeed, the field of oncology is destined to change alongside the increasingly complex developments in molecular medicine and personalized medicine. Oncologists should thus be willing to move beyond their exclusive clinical profession and acquire novel competences, particularly in molecular biology. Finally, joint efforts should be made by pathology and medical oncology communities to promote a more rapid and equal access to novel diagnostic tests able to predict the efficacy of approved targeted agents in cancer patients. Unfortunately, although these cancer drugs are increasingly entering the market, many patients cannot benefit from them because of the unavailability molecular assays in many institutions.

## 8. The integrative side of pathology: computational is the way

Undoubtedly, although the large complexity characterizing the different fields of pathology and herein expounded is significantly contributing to strengthening our knowledge in routine clinical practice, large data storage and processing capabilities are still lacking. Interestingly, following the recently advocated integrative pathology philosophy, the authors of a recent review suggest that the modification of network systems through a strict collaboration with internal information technology services should be mandatory to allow the centralization of medical and computational resources (Mazzanti et al., 2018). In particular, the application of AI to radiographic assessment through the introduction of radiomics is further increasing the complexity of information, and has already demonstrated the great capability to predict surrogate biomarkers (e.g., PD-L1) from staging PET/CT scans when adequately integrated with concurrent NSCLC biopsy (Monaco et al., 2022). Moreover, the progressive application of different "omics" techniques directly on tissue sections is contributing to providing additional crucial information to the already complex picture elaborated by "classic" pathological data, NGS, and AI. In particular, the simultaneous use of digital spatial profiling (DSP) for the study of complex tumour microenvironments (L'Imperio et al., 2022) and next generation proteomics techniques (e.g. MALDI-MS imaging) on both neoplastic (Capitoli et al., 2022; Piga et al., 2021; Galli et al., 2017) and non-neoplastic conditions (Rossi et al., 2021; Capitoli et al., 2020; L'Imperio et al., 2020b, 2019, 2016; Smith et al., 2019, 2017a, 2017b, 2016) is paving the way for a more holistic approach to the field of pathology fields. This could be achievable only though an integrative approach. Finally, the adoption of synoptic instead of narrative reporting could further improve data retrieval from the large datasets of anatomic pathology departments. The potential benefit of this approach could be to help professionals to enrich the information deriving from "omics" and AI, thereby facilitating the application of weakly supervised algorithms that significantly reduce the intervention of pathologists in the annotation phase (Baranov et al., 2019). Thus, the application of a computational and integrative approach to pathology could dramatically ameliorate cancer diagnosis and personalized treatment.

## 9. Conclusions

Anatomic pathology has recently undergone major changes. In fact, with the advent of personalized medicine, modern pathology has gone way beyond traditional morphological evaluations of tissue specimens. The entire spectrum of modern pathology nowadays ranges from preventive, diagnostic, and predictive testing to treatment decision-making and knowledge sharing. Thus, morphological reports no longer represent the finish line but only the starting line in the management of cancer patients. In particular, having to juggle the intricate world of predictive molecular pathology, pathologists now play a crucial role in bridging the gap between oncologists and molecular scientists. Not surprisingly, they have acquired a prominent position in modern MTBs (Fig. 1). Moreover, because knowledge sharing among healthcare professionals is crucial, modern pathologists are now fully embracing the use of innovative technologies and computational devices, working alongside oncologists

to facilitate the whole gamut of patient management. Thus, in this complex scenario, modern pathologists play a central role in the management of cancer patients, not only in the diagnosis but also in the treatment decision making by playing a fundamental part in bridging the gap between oncologists and molecular scientists.

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## CRediT authorship contribution statement

**Pasquale Pisapia:** Conceptualization, Writing – original draft, Project administration, Writing – review & editing, Visualization. **Vincenzo L'Imperio:** Conceptualization, Writing – original draft, Project administration, Writing – review & editing, Visualization. **Francesca Galuppini:** Writing – original draft, Writing – review & editing, Visualization. **Elham Sajjadi:** Writing – original draft, Writing – review & editing, Visualization. **Alessandro Russo:** Writing – original draft, Writing – review & editing, Visualization. **Filippo Fraggetta:** Writing – review & editing, Visualization, Supervision, Project administration. **Giulia d'Amati:** Writing – review & editing, Visualization, Supervision, Project administration. **Giancarlo Troncone:** Writing – review & editing, Visualization, Supervision, Project administration. **Matteo Fassan:** Conceptualization, Writing – review & editing, Visualization, Supervision, Project administration. **Nicola Fusco:** Conceptualization, Writing – review & editing, Visualization, Supervision, Project administration. **Fabio Pagni:** Conceptualization, Writing – review & editing, Visualization, Supervision, Project administration. **Umberto Malapelle:** Conceptualization, Writing – review & editing, Visualization, Supervision, Project administration.

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