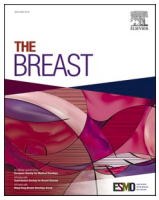
The Breast 81 (2025) 104464

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast



Computational pathology for breast cancer: Where do we stand for prognostic applications?

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A B S T R A C T

The very early days of artificial intelligence (AI) in healthcare are behind us. AI is now spreading in the healthcare sector and is gradually being implemented in routine clinical practice. Driven by the increasing digitization of microscope slides, computational pathology (CPath) is further strengthening the role of AI in the field of oncology. CPath is transforming fundamental research as well as routine clinical practice, both for diagnostic and prognostic applications. In breast cancer, CPath holds the potential to address several unmet clinical needs, particularly in the areas of biomarkers and prognostic tools. Indeed, multiple applications are on their way, ranging from predicting clinically meaningful endpoints to offering alternatives to gene-expression testing and detecting molecular alterations directly from digitized whole slide images. However, to fully harness the potential of CPath, several challenges must be overcome. These include improving the availability of multimodal patient data, advancing the digitalization of pathology laboratories, increasing adoption within the medical community, and navigating regulatory hurdles. This review offers an overview of the current landscape of CPath in breast cancer, highlighting the progress made and the hurdles that remain for its widespread clinical adoption in prognostic applications.

1. An introduction to artificial intelligence in healthcare

This review is dedicated to pathologists, oncologists and medical professionals eager to learn more about the potential of computational pathology (CPath) applied to breast cancer. First, we will provide a brief overview of artificial intelligence (AI) and its key concepts.

1.1. A brief overview of artificial intelligence

AI is a branch of computer science performing tasks that requires human intelligence. It encompasses various fields, including computer vision, which enables computers to automatically analyze images, and natural language processing (NLP), which allows computers to explore and generate human language. A crucial aspect of AI is machine learning (ML), as it enables computers to learn from data and optimize their performance over time. A subset of ML involves deep neural networks (DNN), which are computational models initially inspired by the network of interconnected neurons. DNN consist of connected units organized in multiple layers: an input layer that collects initial data, an output layer that delivers the desired outcome and numerous hidden layers in between that perform most of the computations. Training these networks on large datasets enables them to perform complex tasks, a process known as deep learning (DL). Among DNN, convolutional neural networks (CNN), excel at interpreting medical images, a key area of computer vision. Since around 2016, DL techniques have been state of the art for the analysis of medical images [1].

In DL, two common approaches are supervised and unsupervised learning. The most prevalent method is supervised learning, where models are trained using labeled datasets, where each input image is associated with a correct output label (i.e. ground-truth). The model learns to map input images to the correct outputs by minimizing the error between its prediction and the actual labels. Once trained, the model can then generalize its learnings to make predictions on new, unlabeled and unseen images. While powerful, this supervised approach requires labeled dataset, which can be difficult to obtain. In contrast, unsupervised models are trained on unlabeled dataset, to identify patterns within the image without explicit guidance. Unlike supervised learning, unsupervised learning does not rely on labeled outputs but instead focuses on identifying inherent similarities or differences in the images. A notable example is self-supervised-learning (SSL), a subset of unsupervised learning that automatically generates its own labeled outputs to create a supervised learning-like task. Approaches utilizing SSL for model pre-training, followed by fine-tuning with supervised learning, are gaining traction [2].

This article is part of a special issue entitled: Translational Oncology published in The Breast.

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https://doi.org/10.1016/j.breast.2025.104464
Received 27 September 2024; Received in revised form 24 February 2025; Accepted 26 March 2025
Available online 26 March 2025

In the field of NLP, long short-term memory (LSTM) networks were widely used around 2010 but have since been supplanted by transformers models. Large language models (LLM), such as the well-known OpenAI's ChatGPT, are advanced DL models based on transformer architecture. These models fall under the category of generative AI and have recently become the most popular method for NLP applications. Interestingly, transformers are not confined to NLP as they are also being applied to computer vision tasks through vision transformers (ViT). Recently, ViT have been combined with SSL, to develop a new generation of foundation models. These large models are trained without any input ground-truth and can perform diverse tasks with minimal fine-tuning. They represent significant advancement in AI capabilities and will be discussed in the sections below [2].

1.2. Artificial intelligence for cancer care

AI has a wide range of applications in healthcare [3], particularly in cancer care. Since its inception at the Dartmouth workshop in 1956, AI has witnessed numerous improvements and milestones, such as the first FDA approval of computer-aided-diagnostic (CAD) tools for breast mammography in 2004, IBM Watson winning jeopardy in 2011 and its subsequent application for oncology in 2013, and Google's DeepMind's AI outperforming pathologists in identifying breast cancer in lymph nodes biopsies in 2016. Today, AI can leverage data from electronic health records (EHR) and real-life data from wearables, offering a broader and holistic view of patient health [4]. In the field of image analysis, radiology was one of the first medical discipline to embrace AI, with Geoffrey Hinton, a prominent figure in AI and DL, making a bold prediction stating that "*We should stop training radiologists now. It's just completely obvious that within five years deep learning is going to do better than radiologists*". Even if its prediction has not realized yet, today, AI's role has expanded to other medical domain such as pathology, demonstrating its growing influence across the healthcare sector.

1.3. Computational pathology

1.3.1. An overview of computational pathology

Digital pathology involves converting traditional physical glass slides into digital images, known as whole slide image (WSI). This process encompasses all the aspects of the on-going revolution that is currently transforming the field of pathology worldwide [5,6]. In addition, computational pathology (Cpath), a process that completely relies on digital pathology, aims at developing algorithms to enhance the analysis of WSI through a wide range of different approaches (Fig. 1).

1.3.1.1. Feature-based interpretable models. Initially, ML-based seminal works relied on hand-crafted features designed by humans, which were used to infer interpretable information that was clinically viable [7]. In these approaches, WSI are segmented into meaningful biological structures such as tissues, cells, and nuclei, with each pixel labeled by a distinct class. This fully supervised approach requires time-consuming annotations at the pixel level by pathologists. However, it is highly valuable for improving the interpretability of CPath, as the segmentation of tissues and cells enables the extraction of meaningful morphological characteristics, often referred to human-interpretable features (HIF). For example, segmenting a tumor region allows for the subsequent extraction of a simple HIF, such as the tumor area. Other HIF can be defined after segmentation, such as the nuclear shape, size, and chromatin density, the peri-tumoral density of cancer-associated-fibroblasts or the dispersion of tumor nests. Ultimately, these extracted HIF can be used to predict clinical outcome [8–11](Fig. 1).

1.3.1.2. DL, end-to-end, black box. Now, DL algorithms can provide end-to-end solutions, identifying abstract features without the intervention of a human to design them. Due to their large size, WSI cannot be processed in one single step and must be split into smaller regions called patches or tiles. These patches are used to train supervised DL models, either at the patch level (*i.e.* each patch has a ground-truth label) or at the WSI level (*i.e.* the WSI has the label). In the latter, known as multiple instance learning (MIL), the WSI is divided into patches, and a primary model automatically extracts abstract features from each patch. These features are then combined in a secondary model to calculate abstract feature at the slide level, which is ultimately used to make a prediction. Both methods perform comparably for a multitude of tasks [12]. However, MIL is increasingly preferred because labels for

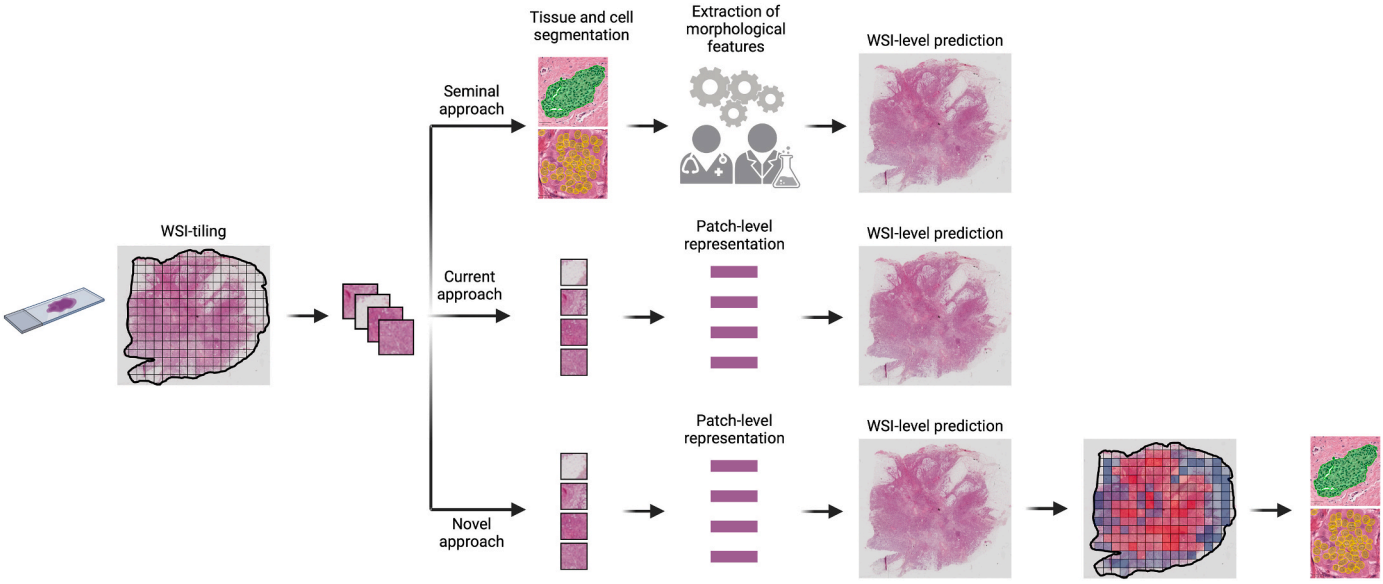

Fig. 1. Different computational pathology approaches to analyze WSI. Seminal approach: the segmentation of cells and tissues (first step) is followed by the creation of human hand-crafted interpretable features (second step) which are then used to make a prediction. Current approaches are using deep-learning end-to-end models that automatically identify features without human intervention to make a prediction at the level of the slide. A Multiple instance learning (MIL) based approach is shown here. Novel approaches are combining old and current methodologies: a deep-learning model is used to make a prediction and then a segmentation approached is applied on important tiles, adding interpretability to the prediction.

WSI are created in the pathology routine and thus easily available, whereas ground-truth at the patch-level must be produced on demand by pathologists for the purpose of the project [13]. Notably, both methods lack contextual information, as each individual patch is considered independently of the others. Recently, several models have been developed to incorporate the spatial context of a patch, including improved MIL architectures such as SparseConvMIL [14], transformer based correlated MIL (TransMIL) [15] and MIL with graph neural networks (GNN-MIL) [16]. These methods are now state-of-the-art in considering the global context of a WSI, where the spatial location of each patch is known.

Instead of evaluating known biomarkers, these end-to-end DL models can leverage unknown features existing in the tissue. However, they exhibit several significant drawbacks. They require vast amounts of training data and suffer from a lack of explainability (i.e., understanding how the model operates) and interpretability (i.e., understanding how predictions are made for a given query), effectively functioning as "black-box" systems that cannot be easily open. In the event of a problem, these models do not readily allow for the identification and understanding of the underlying cause, thereby limiting their implementation in clinical practice. Interestingly, the field is now trending toward combining DL approaches with segmentation-based HIF extraction methods [17,18] (Fig. 1).

1.3.1.3. Foundation models. Recently, foundation models for histopathology have emerged, combining ViT with SLL, and trained on diverse, unlabeled and large amount of pathological data. The foundation model Virchow, trained on more than 1.5 million H&E (haematoxylin and eosin) digital slides [19] exemplifies this trend. The field is booming with various industrials and academic players releasing open-source foundation models [19–26]. Foundation models can be used for a variety of tasks and serve as the building blocks of future models. For instance, when combined with MIL architecture, they enhance the extraction of features at the patch level, thereby improving prediction performances. These models are now state of the art for multiples applications and can sometimes outperform specific models that have been trained for a defined task [27]. However, a very recent benchmark of multiple pathology foundation models showed that they still lack robustness to variations between medical centers [28], highlighting the need for further improvements.

Finally, combining computer vision and NLP has the potential to create remarkable tools for pathologists. For example, foundation model PRISM, built on Virchow, can generate clinical reports [29]. Of interest, Modella.ai has recently built "PathChat", a generative AI model that can deal with images and natural language data, creating a conversational copilot to assist pathologists in analyzing histopathology images and interacting with them [30]. Pathologists should embrace and explore such tools as, with further improvement, they could find various applications in research, education and clinical settings.

1.3.2. Applications of computational pathology

CPath is rapidly transforming the handling of microscopic slides for a plurality of applications.

1.3.2.1. Research applications. In laboratories worldwide, digital slides enable more efficient collaborations and has facilitate the rise of spatial omics technologies, especially for the fundamental and translational research space. After two decades of significant progress in single cell and flow cytometry analyses, access to digital histology slides is adding the crucial spatial context previously missing in research pipelines [31,32]. Initiatives like MOSAIC (Owkin) and HEST-1k are gathering large amounts of spatial data in oncology, promising substantial future discoveries. Due to their cost and complexity, significant challenges remain before these spatial omics applications can be integrated into clinical practice. For the time being, spatial analyses should remain simpler to ensure the use of spatial biomarkers into clinical routine [33].

Additionally, data challenges stimulate the research ecosystem across both industrial and academic sectors. For example, the 2016 Camelyon 16 challenge saw over 32 teams develop approaches to detect breast cancer in lymph node digital slides, while the 2018 BACH challenge focused on automatic classification of breast cancer digital biopsies. In 2022, the TIGER challenge reunited more than 1300 participants across the globe to investigate TILs in breast cancer. These datasets, now publicly available, are contributing significantly to breast cancer research [34,35]. Of note, numerous initiatives are constructing large publicly available datasets, to further stimulate and feed the AI cancer research, including the Cancer Genome Atlas (TCGA), the Clinical Proteomic Tumor Analysis Consortium (CPTAC), the Big Picture and The PathLake initiative [17].

1.3.2.2. Clinical applications. In clinical practice, the adoption of WSI is transforming pathologists' workflow by enabling remote working, facilitating slide sharing for second opinions, and enhancing teaching and knowledge diffusion [36]. CPath is poised to support pathologists with their laborious daily tasks, such as mitoses and grade quantification, lymph nodes screening for metastasis and immunohistochemistry quantification (Ki67, ER, PR, HER2). Several companies have developed and validated such AI diagnosis-assisting tools [37–46]. Here the potential gains in terms of speed are enormous and ultimately patients may benefit from this by having quicker diagnosis and more accurate and reproducible results.

However, the true power of CPath extends beyond the pathologist's routine, toward the oncologist's field. CPath can infer complex and valuable information from WSI, that a pathologist alone cannot, such as predicting patient prognosis, predicting the presence of a molecular actionable alteration or response to a given therapy. With the recent advancement of DL, CPath is slowly reaching the level of clinical evidence required for a use in clinical routine. This will be the focus of the next section.

2. The unmet clinical needs in breast cancer

From now on, we will guide our readers, whether they are cancer researchers, oncologists, or pathologists, through the applications of CPath applied for breast cancer.

Breast cancer is a heterogeneous disease, comprising several distinct subtypes rather than a single entity. These subtypes can be categorized based on different classifications such as histological cancer subtypes (WHO breast cancer 5th edition), hormonal status and phenotype, molecular subtypes [47], genetic alterations and clinical stages (AJCC 8th edition). A precision medicine approach can then be conducted: for each breast cancer subtypes, actionable biomarkers and tests are addressing specific clinical needs to unlock potential targeted therapies (Fig. 2).

For instance, for patients with estrogen receptor (ER)-positive HER2-negative early breast cancer (ER+/HER2- EBC), gene-expression signature tests can guide adjuvant chemotherapy decision. Examples include Oncotype DX (Exact Sciences), MammaPrint (Agendia), Prosigna/PAM50 (Veracyte), Endopredict/EPclin (Myriad Genetics) or Breast Cancer Index (BCI, Biotheranostics). These tests analyze the expression of multiple genes to predict the likelihood of cancer recurrence, helping oncologists to personalize treatment strategy.

Another example is the testing for a germline *BRCA1/BRCA2* mutation, to grant access to PARP inhibitors for patients with advanced or high-risk disease [48].

Despite their clinical utility, these tests require tissue sample from patient, can take several weeks to produce results and are expensive (around 4000 USD per sample for OncotypeDx), thus limiting their accessibility [49]. Most importantly, these tests are only addressing a fraction of the numerous unmet clinical needs in breast cancer management. Emerging technologies such as CPath would offer here a

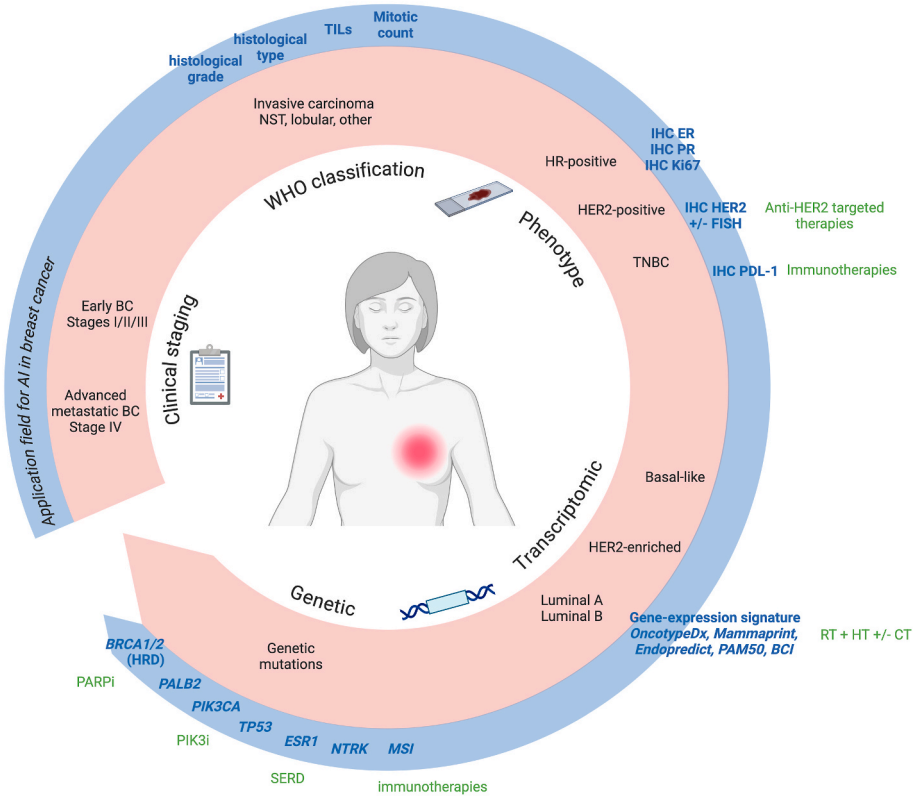

Fig. 2. Overview of the different breast cancer classifications. Non-exhaustive examples of actionable biomarkers and tests and their subsequent therapy are shown. CPath based approaches are being developed to offer valuable alternatives for these current biomarkers and tests (highlighted in blue). BC = breast cancer; CT = chemotherapy; ET = endocrine therapy; RT = radiation therapy; NST = no special type; HR = hormone receptor; ER = estrogen receptor; PR = progesterone receptor; IHC = immunohistochemistry; FISH = fluorescent in situ hybridization; TNBC = triple negative breast cancer; HRD = homologous recombination deficiency; MSI = microsatellite instability; WHO = world health organization. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

valuable alternative, providing faster and more affordable testing strategy.

3. Computational pathology for prognosis in breast cancer

Regarding prognostic applications, CPath has the potential to surpass pathologists capabilities. Two main approaches can be employed for predictions: DL-based end-to-end models, which make predictions based on automatically extracted features but lack interpretability [17], and extraction of meaningful HIF based on pathological knowledge.

3.1. Prediction of survival clinical endpoint and alternatives to gene-expression tests

Several algorithms have been designed to predict meaningful patient outcome, such as overall survival (OS) or metastasis free survival (MFS). Of interest, the role of AI-based detection of tumor infiltrating lymphocytes (TILs) was deeply investigated, especially but not only in triple negative breast cancer (TNBC). For instance, two studies in 2021 proposed ML-based TILs scoring approaches to assess OS in patients with TNBC [50,51]. In addition, Heindl et al., found that TILs spatial heterogeneity was associated with a higher risk of recurrence in ER + breast cancer [52] and Makhlouf et al. showed that stromal and intratumor TILs in early luminal breast cancer correlated with poor clinical outcome [53]. Other prognostic factors detected by AI where shown to correlate with poor patient survival, such as high number of AI-detected mitoses [54] and higher histological grade scoring by DL models [55,56]. Of note, the tumor-stromal ratio also held prognostic value in breast cancer [57,58]. Finally, in their recently published study, Sobral-Leite et al., developed a ductal carcinoma in situ (DCIS) morphometric analysis pipeline that allowed them to elegantly identify DCIS-related features associated with a low risk of progression, such as small-sized ducts, a low number of cells and a low DCIS/stroma ratio [59].

Numerous studies have developed algorithms to predict patient prognosis in ER+/HER2- EBC patients, aiming to explore alternatives to gene-expression signatures [9,18,56,60–67] (Table 1). For example, Wahab et al. developed a prognostic biomarker based on H&E WSI that can stratify ER+/HER2- EBC patients to identify those who may benefit from adjuvant chemotherapy [64]. Boehm et al., developed Orpheus, a transformer model, predicting Oncotype DX recurrence score from H&E WSI(18). Notably, Amgad et al. developed the Histomics Prognostic Signature, an interpretable biomarker that segments tissue and cells to extract epithelial, stromal, immune and spatial interaction features [9]. Pending sufficient level of clinical evidence, these digital tests could significantly enhance accessibility to personalized medicine for breast cancer patients.

3.2. Patient's response to treatment

Algorithms have also been designed to predict patient's response to a specific therapy. For example, in TNBC patients treated by neoadjuvant therapy, AI-based quantification of TILs on H&E WSI was an independent predictor of pathological complete response (pCR) [68]. A similar conclusion was reached in a cohort of HER2-stage IIIB-IIIC breast cancer patients [69]. Interestingly, a computational TILs biomarker achieved 100 % sensitivity for detecting good responders to neoadjuvant therapy in cohorts of triple negative and luminal B breast cancer patients [11]. Another model based on tumor and nuclear segmentation, predicted

Table 1
Non-exhaustive list of industrial players developing models for breast cancer prognosis. EBC = early breast cancer. MFS = metastasis free survival. CT = chemotherapy. DSS = disease specific survival. ODX RS = Oncotype Dx Recurrence Score

Company	Product	Cohorts	Clinical endpoint	Intended use	Sources
Lunit	Lunit Scope	Retrospective, 1343 ER+/HER2- EBC (SMC) Retrospective, 532 ER+/HER2- EBC (TCGA-BC)	Recurrence ODX RS	Guide adjuvant CT	Cho SY (2021) [65]
Stratipath	Stratipath Breast	Retrospective, mostly ER+/HER2- EBC: 256 (ClinseqBC), 559 (TCGA-BC), 1436 (SöS-BC-1), 1670 (CHIME Breast KS Solna) patients. Prospective, mostly ER+/HER2- EBC: 1049/1262 patients (SCAN-B trial NCT02306096) Retrospective, ER+/HER2 EBC: 234 patients	Prediction of histological grade RFS PFS Comparison with Prosigna risk stratification	Guide adjuvant CT, in particular de-escalation	Wang Y (2022) [56] Sharma A (2024) Wang Y (2024) [67]
PreciseDx	Precise Breast	Retrospective, 2075 ER+/HER2- EBC	Recurrence	Guide adjuvant therapy	Fernandez (2022) [61] Fernandez (2024) [62]
Histofy	BRACE marker	Retrospective, 2122 ER+/HER2- EBC Retrospective, 311 ER+/HER2- EBC	MFS DSS	Guide adjuvant CT	Wahab (2023) [64]
Owkin	RlapsRisk BC	Retrospective, 1429 ER+/HER2- EBC Prospective, 889 ER+/HER2- EBC (CANTO trial NCT01993498)	MFS	Guide adjuvant CT	Garberis (2022) [60]
StratifAI	Breast CDx	Retrospective, 5145 ER+/HER2- EBC Retrospective, 452 ER+/HER2- EBC Retrospective, 575 ER+/HER2- EBC	ODX RS	Triaging tool to guide adjuvant CT	Boehm (2024) [18]
ArteraAI	MMAI platform	Prospective, 5259 ER+/HER2- EBC (WSG-planB and ADAPT trials)	Distant Recurrence	Outcome prediction to personalize BC management	Kates-Harbeck (2024) [63]
Ataraxis	Ataraxis Breast	Retrospective, 8161 EBC patients (from 15 datasets)	Risk of cancer-related events Recurrence	Inform treatment decisions in all breast cancer patients	Witowski (2024) [66]

responses to neo-adjuvant therapy in HER2+ and TNBC patients, associating features like higher nuclear intensity and fewer multifocal tumors with pCR [70]. In addition, in 2022, Naylor et al., developed a model on pre-treated biopsies to predict the residual cancer burden (RCB), after neoadjuvant chemotherapy in TNBC patients [71].

3.3. Prediction of molecular alteration

CPath can also infer molecular information directly from H&E WSI. Indeed, the phenotypic characteristics of a tumor are occasionally reflecting specific mutations or genomic alterations. For instance, models were recently developed to predict ER, PR and HER2 on breast cancer H&E images [72,73]. Wang et al., predicted *BRCA* gene mutation in breast cancer from WSI [74] and more recently, Lazard et al. predicted homologous recombination deficiency (HRD) from WSI in luminal breast cancer [75]. Additionally, several models can predict HER2 expression from H&E images [76–78]. Interestingly, Bannier et al., found no significant difference in performance between core biopsies and surgical resection samples, suggesting that the model could be used to predict HER2 status directly from biopsies [78]. As another example, in a large cohort of 3376 breast cancer patients, a DL-based model predicted PD-L1 status from H&E [79]. Predicting molecular alterations from H&E images – biopsies or surgical resections – could offer alternative testing methods for specific mutations, potentially eliminating the need for additional immunohistochemistry or complex molecular biology techniques, a promising alternative in countries with limited resources.

4. Challenges and limitations of computational pathology

While CPath has set high expectations, they are not currently being fulfilled. Several challenges are hindering its global adoption across the world, and these obstacles must be understood to be correctly addressed.

4.1. Multimodal AI

One ongoing challenge for AI in cancer care is the integration of multiple modalities. Every day, oncologists process data from histology, radiology, biology, clinical records and genetic information. The combination of these different data sources is crucial for developing clinically useful AI tools [80]. Few studies are combining two modalities for breast cancer, such as pathology slides with clinical data [63], or pathology slides with genomic data [81]. However, before multimodality becomes a reality, researchers and industry should work on the creation of publicly available large multimodal datasets, which so far, remain too scarce.

4.2. Data availability (histological slide, annotations and multimodal)

Data availability remains a significant limitation. First, large clinical trial-like quality cohorts of patients with histological slides are scarce and expensive. Additionally, most of the time, only one representative slide is available per patient, which underestimates the impact of tumor heterogeneity. Encouraging the development of large, global, open-source data repositories is crucial. Second, getting labels on slides by pathologists is challenging and costly due to the current worldwide shortage of pathologists [82]. While semi-supervised, weakly-supervised, unsupervised learning approaches offer potential solutions, pathologist expertise is essential for developing AI models on pathological slides. These pathologists' annotations should be shared worldwide through open-source repositories. Finally, the lack of large cohorts with multimodal data hinders research on multimodal integration. Online platforms granting access to international clinical trials with comprehensive data (WSI, labels and multimodal data) should be developed to stimulate AI research in oncology.

To address the challenges posed by studying relatively rare cancers, which often involve small cohort sizes, few studies have proposed alternatives to the traditional, labor-intensive process of patient data sharing. Among these, federated learning and swarm learning have emerged as promising approaches. In federated learning, patient data remain securely stored within the hospital's firewall. Local models are trained independently at each site, after which the learned model weights are transmitted to a centralized aggregator node [83]. In swarm learning, on the other hand, models are also trained locally but are combined centrally by blockchain-based coordination, without the need for a central coordinator. This method ensures that the models are not centralized in one single place [84].

4.3. Technical and logistical challenges (digitalization of pathology lab)

The ongoing digitalization of pathology laboratories poses several technical and logistical challenges. Digitalizing a laboratory is costly and reimbursement for digital pathology solutions is not there yet. Laboratories must harmonize their pre-analytical workflows, including tumor sample size, slides thickness, scanner types and staining methods [85]. For example, the addition of saffron to H&E stains in French laboratories (resulting in HES) complicates the generalization of algorithms trained on HES slides. Given the important size of WSI and the high number of slides processed each day for pathological routine diagnosis, whether the storage should be local or decentralized is also a matter of debate. While cloud storage offers scalability, lower initial investment, facilitation of data sharing and back-up solutions, it also raises concerns regarding internet dependency, data sovereignty and security risks. The Health Insurance Portability and Accountability Act (HIPAA) regulation establish standards for the protection of sensitive healthcare information and external providers must comply with HIPAA. The combination of cloud and local storage offers a balanced hybrid solution. Given the slow pace of digitalization in laboratories, they are not yet equipped to support the widespread democratization of digital testing. Therefore, centralized digital testing should be proposed for the time being. However, in ten years, when laboratories will be fully digital and harmonized, digital solutions might be able to operate locally.

4.4. Medical penetration

4.4.1. Interpretability, explainability and scalability

The medical community and oncologists are often hesitant to embrace new technologies like CPath. Importantly, because their treatment decision relies on it, oncologists should be able to understand the underlying technology of the test. Hence, CPath solutions should be explainable and interpretable. Approaches based on HIF are particularly valuable in this context, as they are more readily understandable by both pathologists and oncologists [8,9].

4.4.2. Clinical validation: retrospective versus prospective

To establish the clinical validity of a biomarker aimed at changing patient's care, the gold-standard is the randomized controlled trials (RCT), but these are often very challenging to conduct. For example, in breast cancer, three well-known trials that tested genetic-based classifiers for treatment-decision making are MINDACT, TAILORx and RxPONDER. These three trials required thousands of patients, costed millions of dollars and took almost a decade to complete. Especially in the field of AI, nowadays, innovations are growing fast and therefore, the AI-based test that is being evaluated is likely to become obsolete by the time the RCT is completed. Even though retrospective studies will never reach the clinical evidence of an RCT, a retrospective study conducted with high quality archived specimens from older prospective trial and performed after the delineation of specific pre-specified rules, might be considered as a "prospective-retrospective" study and reach a level IB of evidence [86]. For example, ArteraAI prostate cancer test [87] has recently reached sufficient level of evidence to be incorporated in the National Comprehensive Cancer Network guidelines [88] and has received a Medicare payment rate for it.

4.4.3. Clinical utility

Even after clinical validity has been established, demonstrating the clinical utility of a prognostic biomarker remains a crucial step. This represents the most significant gap between translational research studies focused on the discovery of new biomarkers and those aimed at their implementation in clinical practice. Simply reporting an AUC or a C-index for patient stratification is unlikely to capture the attention of oncologists. However, showing the potential for these biomarkers to guide drug adaptation or influence clinical decision making is far more compelling to the oncological community. Therefore, every new translational and clinical program should be conducted with a multidisciplinary approach, bringing together computational pathologists, pathologists and oncologists.

4.4.4. Existing bias in computational studies

Many CPath research studies still contain biases that limit the expansion of AI in pathology. A recent study [89] identified three main biases: (i) unclear patient cohort details with a lack of clear external validation sets or a mix of training and testing data, (ii) a few studies have more than two distinct sources of data, limiting the clinical applicability of their findings and (iii) a lack of slide-level performance (instead of a patch-level performance) for studies aiming to reach clinical use. Specific recommendations for test dataset are now available and should be followed [90]. In addition, there is an excessive variability in the way researchers assess the performance of their model with significant variability in the metrics employed [91]. Of note, Vaidya et al., showed recently that CPath models used for breast cancer subtyping, had significant performance disparities across demographic groups, highlighting the need for demographic-related bias mitigation [92]. Greater transparency and adherence to recommendations such as the Checklist for Artificial Intelligence in Medical Imaging (CLAIM) or Standards for Reporting of Diagnostic Accuracy Study-AI (STARD-AI) are essential to reach sufficient clinical evidence [93].

4.5. Regulatory bodies, ethical concerns, international initiative for regulations

Finally, the product development pipeline for CPath includes obtaining regulatory approval from agencies such as the In Vitro Diagnostic Medical Device Regulation (IVDR) in Europe and the FDA in the US, achieving the necessary software quality, integrating into laboratory IT infrastructure, and securing reimbursement [90]. Initiatives like the "EcosysteM for Pathology with AI Assistance" (EMPAIA) are gathering all the relevant stakeholders and aim to address these issues and publish guidelines for the development of AI solutions in pathology [94]. In a Delphi study published in 2023, the expert panelists strongly agreed that "meeting regulatory requirements for most AI applications will be a lengthy and costly process" and they were expecting from the regulatory bodies to implement guidelines for AI integration into the pathology workflow. Interestingly, they also acknowledged that ethical concerns would arise "when AI takes over tasks from the pathologist" especially in case of diagnosis error, between the pathologist, the institution, the developer or the industrial vendor [36]. Here again, pathologists and oncologists should be pro-active to propose and implement efficient guidelines rather than waiting for regulatory bodies.

Efforts need to be made to improve data availability, overcome technical and logistical hurdles, ensure clinical and regulatory compliance, mitigate research biases and streamline the product development pipeline. By proactively addressing these issues, the potential of CPath can be fully realized in advancing cancer treatment.

5. Conclusion

To conclude, we believe that computational pathology has the potential to revolutionize and democratize cancer care, not just in breast cancer but across various cancer types [95]. Despite the notable progress, several critical challenges remain. These include the need for large, high-quality datasets, the integration of multimodal data, the establishment of robust technical infrastructures in pathology labs, and overcoming regulatory and ethical hurdles.

To fully realize the potential of CPath, concerted works are needed from researchers, clinicians, industrial leaders and policymakers. Developing and maintaining large, clinical-trial-quality, open-source data repositories with multimodal data is essential. Furthermore, developing interpretable and explainable models will facilitate their subsequent integration into clinical practice. Addressing existing biases

in computational studies and adhering to standardized reporting guidelines will enhance the credibility and applicability of AI models. Finally, proactive engagement with regulatory bodies and the creation of comprehensive guidelines will be crucial in navigating the ethical and legal complexities associated with AI in pathology. By addressing these challenges, computational pathology will revolutionize breast cancer care and improve patient outcomes globally.

CRediT authorship contribution statement

Grégoire Gessain: Writing – review & editing, Writing – original draft, Conceptualization. **Magali Lacroix-Triki:** Writing – review & editing, Conceptualization.

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