Artificial intelligence in cancer pathology: Challenge to meet increasing demands of precision medicine

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Abstract. Clinical efforts on precision medicine are driving the need for accurate diagnostic, new prognostic and novel drug predictive assays to inform patient selection and stratification for disease treatment. Accumulating evidence suggests that a combination of cancer pathology and artificial intelligence (AI) can meet this requirement. In the present review, the past, present and emerging integrations of AI into cancer pathology were comprehensively reviewed, which were divided into four main groups to highlight the roles of AI-integrated cancer pathology in precision medicine. Furthermore, the unsolved problems and future challenges in AI-integrated cancer pathology were also discussed. It was found that, although AI-integrated cancer pathology could enable the amalgamation of complex morphological phenotypes with the multi-omics datasets that drove precision medicine, synergies of cancer pathology with other medical tools could be more promising for the clinic when making an accurate and rapid decision in personalized treatments for patients. It was hypothesized by the authors that exploring the potential advantages of the multimodal integration of cancer pathology, imaging-omics, protein-omics and other-omics, as well as clinical data to decide upon appropriate management and improve patient outcomes may be the most challenging issue of cancer precision medicine in the future.

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Abbreviations: AI, artificial intelligence; ANN, artificial neural network; BC, breast cancer; CC, cervical cancer; CNN, convolutional neural network; CP, cancer prognostication; CRC, colorectal cancer; DA, diagnostic accuracy; DL, deep learning; DP, digital pathology; DPr, disease prevention; EM, electron microscopy; FCN, fully CNNs; GSC, genomic sequencing classifier; HCC, hepatocellular carcinoma; LC, lung cancer; LUAD, lung adenocarcinoma; MIBC, muscle-invasive bladder cancer; MIL, multiple-instance learning; ML, machine learning; MP, molecular pathology; NSCLC, non-small cell LC; PCa, prostate cancer; pCR, pathological complete response; SL, swarm learning; TCGA, The Cancer Genome Atlas; TILs, tumor-infiltrating lymphocytes; WSIs, whole-slide images

Key words: artificial intelligence, cancer pathology, diagnosis, precision medicine, prognosis

Contents

1. Introduction

It was estimated that there were >19 million new cancer cases and 9 million cancer-related deaths in 2020 worldwide. The top five cancer sites, based on the global cancer incidence, are as follows: Female breast cancer (BC), lung cancer (LC), colorectal cancer (CRC), prostate cancer (PCa) and stomach cancer, and more than half of cancer deaths globally are attributed to these cancer types (World Health Organization. Cancer Today. 2020; https://gco.iarc.fr/). In China, a growing cancer burden was unexpectedly observed, and nearly 3 million cancer deaths and >4 million individuals were diagnosed with cancer in 2020. Accurate diagnosis and personalized cancer therapy are the keys to improving the cancer prognosis for every patient. With the promise of an estimated numerical

prognosis for patients with cancer, AI has been proposed as a prominent way to improve pathological diagnostic accuracy (DA) and cancer prognostication (CP). Over the past decades, although the exploration and exploitation of AI in cancer pathology has evolved substantially, their generations, interpretations and impact on patients have remained incompletely understood by oncologists. In the present study, the published literature on Google Scholar and PubMed were searched using the following terms: 'AI' AND 'pathology' AND 'cancer', or 'machine learning (ML)' AND 'pathology' AND 'cancer', or 'deep learning' AND 'pathology' AND 'cancer'. The present review includes an overview of the roles of AI-integrated cancer pathology in precision medicine by summarizing the rationale for its use, clarifying recent innovations and grouping the main applications, as well as discussing the challenges for AI-integrated cancer pathology-based individualized treatment.

2. Artificial intelligence (AI)

AI is defined as the ability of a machine to simulate, extend and expand human cognition, and has the most features suggestive of human intelligence, to decide upon an action to achieve the desired goal. Initially proposed in 1950 by Turing with 'Can Machines Think', and subsequently coined in 1956 by McCarthy (Fig. 1), AI was originally described as being able to 'simulate intelligence'. With the gradual advent of ML based on computational algorithms and the following computational intelligence, the more power of the decision-making pattern AI was endued with, and the more diverse, complex or esoteric fields AI was involved in, a marked impact was made on modern civilization, namely on Industrial Revolution 4.0 (1). Deep learning (DL) introduced in 1986 by Dechter is by far the most common subtype of ML, and represents computational models originating from artificial neural networks (ANNs) to derive progressively higher-order features from data in the form of multiple non-linear layers (Fig. 2) (1). Inspired by neurobiology, DL is composed of units that compute a weighted sum of the multiple inputs (referred to as the *pre-activation*) and transforms the results non-linearly, which includes automatic learning and hierarchical representation on multiple levels (2). DL has been employed in nearly all scientific areas, especially in medical imaging, including cancer pathology (the cornerstone of cancer medicine), which has yielded important results that paved the way for the development of the convolutional neural network (CNN), generative adversarial network (GAN), auto encode and so on, to meet the demands of specific biomedical applications for precision oncology.

3. Digital pathology (DP)

Defined as an image-based approach, DP aims to acquire, manage, interpret and distribute pathology information in a computer-empowered manner, to extract and analyze pathological visual data. Since the introduction of telepathology in 1986 by Weinstein, the emergence of whole slide images (WSIs) in the 1990s, and other digital images (Electronic microscope digital images), has boosted the prosperity of the DP era (Fig. 1A) (3). Efforts have been devoted to improving the scanning speed and the accuracy of images, which are the two major issues affecting the throughout performance of WSIs. Notably, GAN, an unsupervised technique proposed by Goodfellow *et al* (4) in 2014, was composed of two competing models: i) A generative model G capturing the data distribution; and ii) a discriminative model D, which made likelihood estimations on the training data rather than G. With respect to this, Fanous and Popescu (5) reported a new method in 2022 (referred to as GANscan) to significantly increase the scanning speed of the whole slide scanner and to correct any defocusing by integrating the Pix2Pix image translation framework and GAN-based model.

Notably, WSIs provide an enabling AI platform for generating a rich variety of novel ecosystems in DP, which is known as Pathomics. Pathomics is an AI-based multi-systems integration methodology to understand cellular interactions and signaling by analyzing relevant data from tissues and cells. With the emergence of Pathomics, integration of AI into the DP workflow has achieved some breakthroughs in cancer pathology. For example, in MICCAI 2014 (Table I), the brain tumor digital pathology challenge, including two sub-challenges (classification and automated segmentation), was posted. In this regard, Barker *et al* (6) demonstrated a novel method using local representative tiles, decided diagnostically by an elastic net classifier, for automated classification in brain cancer cases, which exhibited high accuracy for diagnosis as well as structural stability and a robustness for varying parameters, implying that it may be useful for automatic differentiation of the two subtypes of brain cancer (glioblastoma multiforme and lower grade glioma) (Table II). In another example, multiple-instance learning (MIL), first proposed by Dietterich *et al* in 1997, is a variation on supervised learning. In 2019, Campanella *et al* (7) presented the MIL-RNN models in the analysis of three datasets (including PCa, basal cell carcinoma of the skin and BC metastases to axillary lymph nodes datasets) of 44,732 WSIs from 15,187 patients, in which MIL-based residual neural network (ResNet)34 models were used to classify tiles. Then, semantically rich tile-level feature representations were generated, which integrated the information across the WSIs through the RNN models and achieved the final classification result. This system was shown to be able to train accurate classification models at an unprecedented scale, providing the cornerstone for the evolution of computational decision support systems in clinical practice (Fig. 1).

Notably, one of the biggest challenges in neuroanatomy [the automatic segmentation of neuronal structures presented in stacks of electron microscopy (EM) images] at ISBI 2012 was won by Ciresan *et al* (8) by employing a special type of deep ANN as a pixel classifier (Table I). However, there were two key disadvantages to the strategy raised by Ciresan *et al*, which were that it was slow and required a trade-off between localization accuracy and the use of context. Fortunately, a noteworthy finding was reported by Shelhamer *et al* (9) in 2017, where the fully convolutional networks (FCN) model could convert semantic-level images into pixel-level images using a convolution layer, instead of the full connection layer of the original segmentation network, which promoted the rapid development of image segmentation. For instance, Signaevsky *et al* (10) revealed that the FCN implemented in PyTorch was efficient and well suited for the practical application of WSIs derived

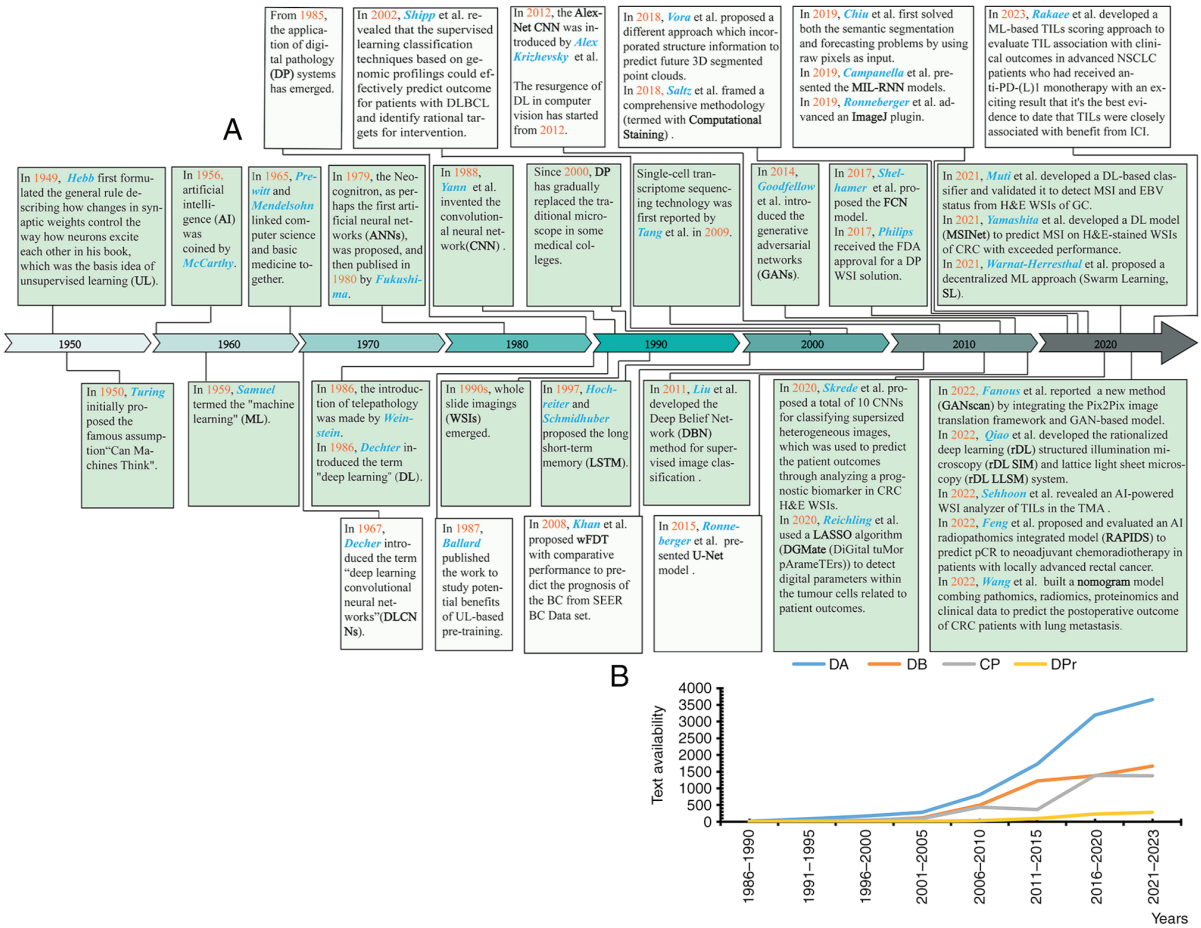

Figure 1. (A) Timeline of the terms used and hallmarks in the field of AI, which influenced the development of cancer pathology. (B) The number of papers retrieved according the four categories of principal tasks of integration of AI and cancer pathology in precision medicine, including: DA, CP, DB and DPr. AI, artificial intelligence; ANNs, artificial neural networks; CNN, convolutional neural network; CP, cancer prognostication; DA, diagnostic accuracy; DB, drug benefit; DBN, deep belief network; DGMate, DiGital tuMor pArameTErs; DLBCL, diffuse large B-cell lymphoma; DP, digital pathology; DPr, disease prevention; GANs, generative adversarial networks; LLSM, lattice light sheet microscopy; LSTM, long short-term memory; ML, machine learning; NSCLC, non-small cell lung cancer; rDL, rationalized DL; SL, swarm learning; SIM, structured illumination microscopy; TILs, tumor-infiltrating lymphocytes; UL, unsupervised learning; WSIs, whole slide images.

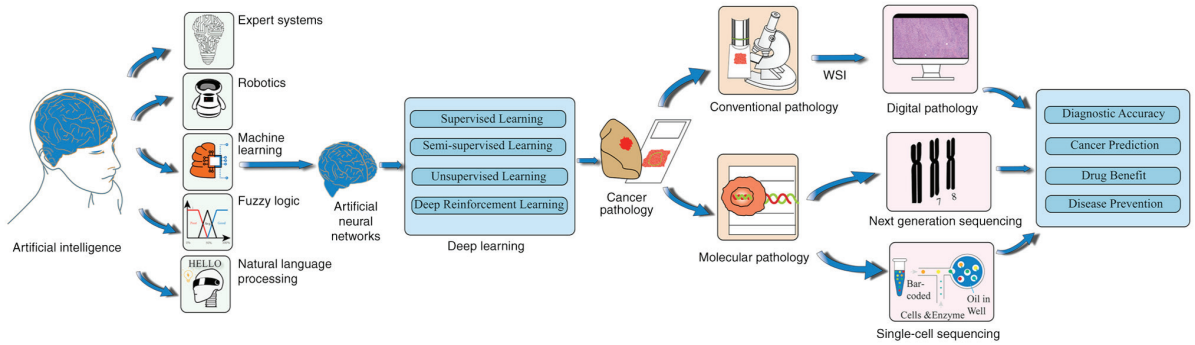

Figure 2. General framework of AI integrating into cancer pathology. AI encompasses a wide variety of strategies (such as, expert system, robotics, fuzzy logic and nature language processing), in which ML is used to make a prediction emulating what an intelligent human may do in the same situation. DL is a subset of a larger group of ML methods developed from artificial neural networks, which consist of algorithms with hierarchical processing layers that perform non-linear transformations to represent and learn data characteristics effectively. Integrating DL and other ML approaches into cancer pathology, which is mainly composed of conventional pathology and MP, can reinforce the ability of oncologists to understand and address the role of cancer pathology in precision medicine pertaining to diagnostic accuracy, cancer prognostication, drug benefit and disease prevention. AI, artificial intelligence; DL, deep learning; ML, machine learning; WSI, whole slide image.

from 22 autopsy brains from patients with tauopathies, which produced high precision and recall in naïve WSI semantic segmentation. Yi *et al* (11) also demonstrated that a finely-tuned FCN could be applied to analyze the microvessels of H&E stained histology images from patients with lung adenocarcinoma (LUAD) for prognostication. As a result of this FCN

Table I. Overview of the principal challenges related to digital pathology (as of May 2023).

Year	Name of the challenge	Tissue	Staining	Aims of the challenge	Provided ground-truth
2012	ISBI2012 https://imagej.net/events/isbi-2012-segmentation-challenge	Neuro	-	Automatic segmentation of neural structures	Binary labels
2013	AMIDA13 https://www.isi.uu.nl/research/challenges/	BC	H&E	Assessment of mitosis detection algorithms (51,52)	-
2014	ISBI2014 https://archives.embs.org/wp-content/archives/ISBI/2014/?page_id=17	Cervix, uterus	PAP	Extracting the boundaries of individual cytoplasm and nuclei from overlapping cervical cytology images	Counting mitosis
2014	ICPR https://mitos-atypia-14.grand-challenge.org	BC	H&E	Mitosis detection, nuclear atypia scoring	Centroids of mitosis, nuclear atypia scoring
2015	GlaS (TIA) https://warwick.ac.uk/fac/sci/dcs/research/tia/glascontest/	Gland	H&E	Gland segmentation	Binary masks
2015	BioImaging2015 http://www.bioimaging2015.ineb.up.pt/challenge_overview.html	BC	H&E	Cancer classification	Labels
2016	TUMAC https://tupac.grand-challenge.org/	BC	H&E	Prediction of tumor proliferation scores	Tumor proliferation scoring, molecular proliferation scoring
2016	HER2 Scoring https://warwick.ac.uk/fac/sci/dcs/research/tia/her2contest	BC	IHC	HER2 scoring	HER2 scoring and a percentage score given by pathologists
2016	CAMELYON'16 https://camelyon16.grand-challenge.org/ (Closed)	BC	H&E	Detection of cancer metastasis (53)	Annotated contours, binary masks
2017	CAMELYON'17 https://camelyon17.grand-challenge.org	BC	H&E	Detection of cancer metastasis	Metastases annotations in WSIs, patient pathological node stage labeling
2017	ISBI 2017 https://biomedicalimaging.org/2017/	TC	H&E, IHC	Tissue microarray analysis in TC diagnosis (54)	-
2018	ICIAR 2018 (BACH) https://iciar2018-challenge.grand-challenge.org	BC	H&E	Classification and pixel-wise labelling of WSIs	Pixel-wise labels
2018	PatchCamelyon https://patchcamelyon.grand-challenge.org	Lymph node	H&E	Metastasis detection	Binary label indicating presence of metastatic tissue
2019	ACDC-LungHP https://acdc-lunghp.grand-challenge.org	LC	H&E	Cancer detection, assessment of tumor proliferation	Annotation of cancer regions
2019	ANHIR https://anhir.grand-challenge.org/Intro/	LC, BC	H&E, IHC	Comparing the accuracy and the speed of automatic non-linear registration methods on a set of large images from the same tissue samples but stained with different biomarkers	-

Table I. Continued.

Year	Name of the challenge	Tissue	Staining	Aims of the challenge	Provided ground-truth
2019	Digestpath2019 https://digestpath2019.grand-challenge.org/	CRC	H&E	Evaluation of signet ring cells and colonoscopy tissue screening	Number of signet ring cell for each patch and tissue segmentation
2019	LYSTO https://lysto.grand-challenge.org/LYSTO	BC, CRC and PCa	IHC	Assessment of lymphocytes	Number of lympho cytes for each patch
2019	PAIP https://paip2019.grand-challenge.org/Home/	LC	H&E	LC segmentation	Tumor area segmentation, viable tumor area
2019	CodaLab (ISBI 2019) https://competitions.codalab.org/competitions/20395#learn_the_details-overview	Blood	-	Cell classification	Marked by the expert oncologist
2019	LYON https://lyon19.grand-challenge.org/Home/	BC, CRC and PCa	IHC	Lymphocyte detection	-
2019	Gleason https://gleason2019.grand-challenge.org	PCa	H&E	Gleason grading (tissue microarray)	Maps and labels
2019	SPIE-AAPM-NCI BreastPathQ https://breastpathq.grand-challenge.org/	BC	H&E	Determination of cancer cellularity	Tumor rating
2020	ECDP2020 https://ecdp2020.grand-challenge.org/Home/	BC	H&E	Identifying $HER2^+$ from HER2	-
2021	BCNB https://bcnb.grand-challenge.org/	BC	H&E	Axillary lymph node metastasis status	Annotation of cancer regions
2021	PANDA https://panda.grand-challenge.org/	PCa	H&E	Gleason grading	Tumor regional score grading
2021	MIDOG 2021 https://midog2021.grand-challenge.org/	Various tumors, including BC	H&E	Mitosis detection	Labels
2021	TIGER https://tiger.grand-challenge.org/	BC	H&E	Automatic quantification of TILs in BC	Tumor region segmentation
2021	BCSS https://bcsegmentation.grand-challenge.org/	BC	-	BC semantic segmentation	Image segmentation
2022	AGGC22 https://aggc22.grand-challenge.org/	PCa	H&E	Gleason grading	Identifying the cellular and glandular patterns for Gleason grading
2022	BCI https://bci.grand-challenge.org/	BC	H&E, IHC	Identify $HER2^+$	Peak signal to noise ratio and structural similarity

Table I. Continued.

Year	Name of the challenge	Tissue	Staining	Aims of the challenge	Provided ground-truth
2022	CoNIC https://conic-challenge.grand-challenge.org/	CRC	-	Nuclear segmentation and classification, prediction of cell composition	-
2022	MIDOG2022 https://midog2022.grand-challenge.org/	-	H&E	Mitosis detection	Labels
2022	WSSS4LUAD https://wsss4luad.grand-challenge.org/	LUAD	H&E	Tissue semantic segmentation	Image annotation
2022	Neurips22 https://neurips22-cellseg.grand-challenge.org/	-	H&E	Cell semantic segmentation	Image segmentation
2022	ENDO-AID https://endo-aid.grand-challenge.org/	Endometrial carcinoma	H&E	Prediction of cancer types	Labels
2023	PAIP2023 https://2023paip.grand-challenge.org/	Colon and pancreatic cancer	H&E	Tumor cellularity prediction	Counting tumor cells

BC, breast cancer; CRC, colorectal cancer; IHC, immunohistochemistry; LC, lung cancer; LUAD, lung adenocarcinoma; PCa, prostate cancer; TC, thyroid cancer; TILs, tumor-infiltrating lymphocytes; WSIs, whole slide images.

development, the U-Net model was presented in 2015 by Ronneberger *et al* (12) who, through modifying and extending the FCN, which supported automatic recognition and precise segmentation of characteristic lesions in EM stacks, beat the network presented by Ciresan *et al* (8) at ISBI 2015 (Table I). Furthermore, building on past efforts, Ronneberger *et al* developed an ImageJ plugin that enabled non-ML practitioners to solve problems with U-Net on either a local computer or a remote server/cloud service, which provided a generic DL-based software package for 2D and 3D cell detection and segmentation (12,13). A case in point, Lee *et al* (14) in 2020 used the modified U-Net to perform spatial analysis for the tumor microenvironment (TME) in WSIs from breast invasive carcinoma cases to replenish cancer classification and prediction, which demonstrated the effectiveness of the U-Net approach and the quantitative estimates derived from the spatial analysis. In addition, U-Net was proposed to aid the epidermis segmentation task on WSIs from malignant melanoma by Oskal *et al* (15), in which a superior performance of U-Net compared with existing techniques was observed.

In short, AI has been involved in the growth of DP, which has indicated that AI may bring a future of intelligent diagnostic robots.

4. Molecular pathology (MP)

In addition to the use of conventional pathology as the basis for DP, AI has also demonstrated unparalleled advantages and potential in MP, which is a sub-microscopic discipline of pathology. MP predicts risk, facilitates diagnosis and improves prognostication based on a complete understanding of the biological impact of specific molecular variants, mutations and dysregulations in diseases. MP techniques, which were rooted in fundamental molecular biology discoveries of the 1940s to 1980s (for example, PCR developed by Mullis in the 1980s), have moved from genomics to proteomics [such as next-generation sequencing, single cell RNA sequencing, fluorescence in situ hybridization, NMR spectroscopy and iTRAQ-MALDI-MS/MS], which has been driven by an increasing number of druggable targets and predictive biomarkers. Undeniably, AI fostered the development of MP, which was mainly encompassed by molecular profiles for risk prediction and molecular diagnostics, especially genomic diagnostics (16). For example, Woerl *et al* (17) formulated a novel ResNet-based approach (termed mibCNN) to predict the molecular subtype of muscle-invasive bladder cancer (MIBC) by analyzing two datasets of WSIs from H&E staining alone. The results demonstrated that DL could be trained to predict the significant molecular characteristics of MIBC from digital images derived from H&E slides only, potentially resulting in an improvement in managing this disease. Similarly, Schrammen *et al* (18) described a comparative performance with a state-of-the-art method (referred to as the slide-level assessment model), which simultaneously detected tumors and predicted the genetic alterations (including microsatellite instability/mismatch repair deficiency status and BRAF mutational status) of CRC from H&E-stained histopathological WSIs.

Table II. Overview of the principal papers AI-integrated cancer pathology for four main tasks, including DA, CP, DB and DPr (as of May 2023).

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Shipp *et al*, 2002	The supervised learning classification techniques based on genomic profiling could effectively predict outcome for patients with DLBCL and identify rational targets for intervention.	H&E, IHC, genomic microarrays	DLBCL	CP & DB	(55)
Khan *et al*, 2008	wFDT demonstrated comparative performance to predict the prognosis of BC from the SEER BC dataset.	H&E	BC	CP	(56)
Fatakdawala *et al*, 2010	EMaGACO was applied to evaluate lymphocytic infiltration on $HER2^+$ BC WSIs with comparative performance.	H&E	BC	DA	(57)
Sertel *et al*, 2010	A computer-aided detection system for automated identification of CB cells from H&E stained FL tissue samples was presented with a promising 80.7% detection accuracy.	H&E	FL	DA	(58)
Dundar *et al*, 2011	A prototype system for automatically classifying breast microscopic tissues to distinguish between UDH and actionable subtypes (ADH and DCIS) was observed with competitive performance.	H&E	IBL	DA	(59)
Tuominen *et al*, 2012	The ImmunoMembrane method based on AI technology was used to improve the diagnostic accuracy of HER2 IHC from BC.	IHC	BC	DA	(60)
Gertych *et al*, 2012	CF-SVM classifiers were delineated to improve the risk stratification of CC by evaluating dual p16/Ki67 nuclear ICC based on PAP.	PAP, ICC	CC	CP	(61)
Doyle *et al*, 2012	A cascaded (CAS) approach was proposed to classify prostate biopsy tissue samples based on H&E stained WSIs with comparative performance.	H&E	PCa	DA	(62)
Wang *et al*, 2014	A light CNN model based on a combination of a CNN model and handcrafted features (morphology, color and texture features) was proposed to detect mitosis in H&E stained WSIs to predict disease aggressiveness and patient with BC outcome.	H&E	BC	CP	(63)
Lewis *et al*, 2014	The classifier (QuHbIC) was validated to predict outcomes of patients using the information from a H&E stained microarray cohort of $p16^+$ OSCC cases.	H&E, TMA	OSCC	CP	(64)
Sirinukunwattana *et al*, 2015	Outperformance was observed in an experiment using a spatially constrained CNN to detect the malignant epithelial nuclei in H&E stained WSIs of BC and CRC cases.	H&E	BC & CRC	DA	(65)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Yuan *et al*, 2015	An unbiased methodology was proposed to model the spatial distribution of TILs in TNBC to predict prognosis and treatment options.	H&E	TNBC	CP & DB	(66)
Veta *et al*, 2015	The results from the Assessment of Mitosis Detection Algorithms 2013 (AMIDA13) challenge were presented. The challenge was based on a dataset consisting of 12 training and 11 testing subjects, with >1,000 annotated mitotic figures by multiple observers.	H&E	BC	DA	(52)
Paul, 2015	A fast and accurate approach for automatic mitosis detection from BC histopathological images was proposed with a favorable result.	H&E	BC	DA	(51)
Xie *et al*, 2015	Used a CNN-based voting method to localize nucleus centroids with heavy cluttering and morphologic variations in microscopy images.	H&E, IHC	Neuroendocrine tumor	DA	(67)
Sirinukunwattana *et al*, 2016	Joint detection and classification of the proposed SC-CNN and NEP coupled with CNN could detect and classify cell nuclei in histopathology images of cancerous tissue more accurately.	H&E	CRC	DA	(68)
Romo-Bucheli *et al*, 2016	Developed a DL classifier to automatically identify tubule nuclei and predict Oncotype DX risk from WSIs of ER^+ BC.	H&E	BC	DA & DB	(69)
Xu *et al*, 2016	A DL strategy, SSAE, was presented to efficiently detect nuclei on high-resolution histopathological images of BC.	H&E	BC	DA	(70)
Turkki *et al*, 2016	A CNN-based approach was applied to quantify immune cell infiltration in BC samples using only basic morphology staining.	H&E, IHC	BC	DA	(71)
Ali *et al*, 2016	An image-processing pipeline based on SVM was used to accurately diagnose and classify lymphocyte cells from H&E stained WSIs to predict the response to neoadjuvant chemotherapy and the outcome of the patient.	H&E	BC	DA, CP & DB	(72)
Bartsch *et al*, 2016	A genetic programming algorithm was applied to evolve classifier mathematical models for outcome prediction, which predicted recurrence in non-muscle invasive UC of the bladder.	Gene profiling	BLCA	DB & CP	(73)
Yu *et al*, 2016	Regularized machine learning methods were used to analyze information from H&E stained and TMA-based WSIs of LC to predict prognosis of patients.	H&E, TMA	LC	CP	(74)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Barker *et al*, 2016	A novel method, using local representative tiles determined diagnostically by an Elastic Net classifier for automated classification in brain cancer cases, demonstrated high accuracy for diagnosis as well as being structurally stable and robust for varying parameters, implying that it could be used to automatically differentiate between GBM and LGG.	H&E	GBM, LGG	DA	(6)
Ali *et al*, 2017	Lymphocyte density in pre-treatment biopsies was validated as an independent predictor of pCR in BC by analyzing the H&E stained WSIs using an SVM-based approach.	H&E	BC	DA, CP & DB	(75)
Ehteshami Bejnordi *et al*, 2017	7 automatic DL algorithms showed outperformance in the CAMELYON16 researcher challenge competition, which could be used to improve diagnostic accuracy and efficiency in detecting metastasis in female BC lymph node tissue sections.	H&E	BC	DA	(53)
Lu *et al*, 2017	The OHbIC was constructed to predict outcomes of patients with OSCC from H&E-based WSIs.	H&E	OSCC	CP	(76)
Gecer *et al*, 2018	A system based on the combination of four FCNs and one CNN was presented to detect and classify BCs in WSIs with outperformance.	H&E	BC	DA	(77)
Haider *et al*, 2018	SIMMS algorithm was observed to be useful for predicting phenotypes in five cancer types.	H&E	Five cancer types, including BC	CP	(45)
Yoshida *et al*, 2018	The e-Pathologist image analysis software was proposed to automatically classify GC on H&E stained WSIs with comparative performance to pathologists.	H&E	GC	DA	(78)
Bo *et al*, 2018	A deep residual network with 50 layers was used auto-classify GC, resulting in improving the generalization performance.	H&E	GC	DA	(79)
Ichimasa *et al*, 2018	An artificial intelligence model was generated to help in deciding the additional surgery after endoscopic resection of T1 CRC with the presence of lymph node metastasis.	H&E	CRC	CP & DPr	(80)
Mezheyeuski *et al*, 2018	A fluorescence-based multiplexed immunohistochemical method in combination with a multispectral imaging system was used to quantify immune infiltrates *in situ* in an NSCLC TMA.	H&E, IHC	LC	DA	(81)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Yi *et al*, 2018	A microvessel prediction method using fully CNNs was proposed and evaluated on H&E stained WSIs from LUAD.	H&E, IHC	LUAD	DA	(11)
Mobadersany *et al*, 2018	A computational approach combining the power of adaptive ML algorithms with traditional survival models was proposed to predict glioma outcomes by integrating information from WSIs and genomic profiling, which surpassed current-level performance.	H&E, genomic profiling	Gliomas	CP	(82)
Saltz *et al*, 2018	A comprehensive methodology (termed Computational Staining) based on CNNs was framed to map TILs and analyze the molecular and clinical correlation with TILs from H&E-stained WSIs containing 13 TCGA cancer types. TIL map structural patterns were generated with a competitive performance, which revealed that TILs patterns were associated with tumor and immune molecular features, cancer type and survival, which laid a new milestone for TME research.	H&E	13 TCGA cancer types	DA, DB & CP	(21)
Ching *et al*, 2018	A new neural network framework called Cox-nnet was applied to predict patient outcomes accurately and efficiently from 10 high-throughput transcriptome TGCA datasets.	Gene profiling	10 TCGA cancer datasets	CP	(41)
Katzman *et al*, 2018	DeepSurv, a Cox proportional hazards deep neural network and state-of-the-art survival method, was used to explore, understand and predict the effects of patient characteristics on the risk of failure.	H&E	Cancer	CP	(42)
Chaudhary *et al*, 2018	A DL-based model of HCC was proposed to predict HCC survival from 6 patient cohorts by integrating multi-omics data (RNAseq, miRNA sequencing, and methylation data from the TCGA) with outperformance.	Gene profiling	HCC	CP	(83)
Günakan *et al*, 2019	A Naive Bayesian ML algorithm was used to construct a model for predicting lymph node metastasis in patients with endometrial cancer.	H&E	UCEC	CP	(84)
Tabl *et al*, 2019	A hierarchical ML system could predict the 5-year survival of patients who underwent specific therapy and identify gene biomarkers to guide the treatment of BC.	Gene profiling	BC	DA, CP & DB	(46)
Turkki *et al*, 2019	An ML method was used to predict the outcome of patients with BC by analyzing the information from TMAs.	TMA	BC	CP	(85)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Fang *et al*, 2019	A CNN with deep generalized multi-instance learning was used to classify differentiation degree (poorly and well/moderately) and lauren type (intestinal, diffuse and mixed) in GC with a favorable result.	H&E	GC	DA	(86)
Mori and Miwa, 2019	VGG16 based on CNN was observed to predict the invasive progression in gastric signet-ring cell carcinoma component to distinguish between intramucosal or advanced disease.	H&E, IHC	GC	DA	(87)
Leon *et al*, 2019	Two approaches based on CNN were proposed to classify benign or malignant cancer from stomach biopsy specimens.	H&E	GC	DA	(88)
Wang *et al*, 2019	An automated cell type classification pipeline, ConvPath, was proposed to identify TME-related features.	H&E	LUAD	DA	(89)
Aprupe *et al*, 2019	A CNN-based immune cell detection and quantification method was applied on IHC WSIs from LC, which demonstrated a similar performance to humans.	IHC	LC	DB	(90)
Dihge *et al*, 2019	Seven machine-learning models were proposed to predict lymph node metastasis of BC from the combined information of clinicopathological characteristics, gene expression data and mixed features, as well as SLNB, which demonstrated comparable accuracy and identified more node-negative patients, resulting in reducing the rates of SLNB for patients at low risk of nodal involvement.	H&E	BC	CP & DPr	(91)
Nir *et al*, 2019	Classifier performance was evaluated by its accuracy, sensitivity and specificity in the detection of PCa in H&E stained TMAs.	H&E, TMA	PCa	DA & CP	(92)
Campanella *et al*, 2019	A multiple instance learning-based DL system (MIL-RNN models) was presented, with accurate classification of cancer types from 3 datasets of 44,732 H&E stained WSIs from 15,187 patients (PCa, BCC and BC metastasizing to axillary lymph nodes).	H&E,	PCa, BCC and BC	DA	(7)
Courtiol *et al*, 2019	A new approach based on DCNN, termed MesoNet, was developed to accurately predict the overall survival of patients with MM from WSIs.	H&E	MM	DA	(93)
Achi *et al*, 2019	An attempted build of a lymphoma diagnostic model for four diagnostic categories using DL with a CNN algorithm: Benign lymph node, DLBCL, BL and SLL.	H&E	Lymphoma	DA	(94)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Gao *et al*, 2019	A novel DL-based framework deep cancer subtype classification (DeepCC) was used to classify cancer molecular subtypes using TCGA RNA-Seq datasets.	Gene profiling	CRC and BC	DA & DB	(36)
Rodner *et al*, 2019	An FCN-based automated image analysis algorithm was proposed to discriminate between HNCA and non-cancerous epithelium with a significant performance.	H&E, IHC	HNCA	DA	(95)
Hu *et al*, 2019	A DL-based visual evaluation algorithm was developed to automatically recognize cervical precancer or cancer with a favorable result.	H&E	CC	DA & DPr	(96)
Tian *et al*, 2019	An ML algorithm (Random Forest) was applied to build a risk stratification model for cervical precursor lesions based on $CIN2^+$ enriched biomarkers from the capture-based NGS of 34 paired samples (including exfoliated cervical samples, cervical tissues and others).	Gene profiling	CC	CP	(97)
Newman *et al*, 2019	CIBERSORTx, an ML method, was introduced to infer cell-type-specific gene expression profiles from bulk tissue transcriptomes, which revealed cell-type-specific phenotypic states linked to distinct driver mutations and response to immune checkpoint blockade.	Gene profiling	Multiple cancer types, including malignant melanoma	DB	(98)
Oskal *et al*, 2019	A U-net based approach to epidermal tissue segmentation in H&E stained WSIs from malignant melanoma was proposed with a superior performance compared with existing techniques.	H&E	Malignant melanoma	DA	(15)
van IJzendoorn *et al*, 2019	Various ML methods were used to identify novel diagnostic and prognostic markers and therapeutic targets for STS from multiple STS gene expression datasets.	Gene profiling	STS	DA, CP& DB	(44)
Bulik-Sullivan *et al*, 2019	A DL-based computational model of antigen presentation named EDGE was proposed to predict neoantigens in a large HLA peptide and genomic dataset from various human tumors, resulting in increasing the positive predictive value of HLA antigen prediction by up to ninefold, which suggested that EDGE could enable an improved ability to develop neoantigen-targeted immunotherapies for patients with cancer.	Gene profiling	Various cancer types	DB	(47)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Huang *et al*, 2020	A set of DL-based models, including Cox-nnet, DeepSurv and a method proposed by Huang *et al* named AECOX (AutoEncoder with Cox regression network) were applied to capture the information from RNA-seq data to predict the survival prognosis of patients across 12 cancer types with superior performances.	Gene profiling	12 cancer types	CP	(43)
Choi *et al*, 2020	A robust GSC based on whole transcriptome RNAseq was designed to validate gene expressions values predicting clinicopathological features using several LC cohorts.	Gene profiling	LC	CP & DB	(20)
Saillard *et al*, 2020	Two DL algorithm models based on H&E stained WSIs outperformed a prediction of the survival of patients with HCC treated by surgical resection.	H&E	HCC	CP	(99)
Dietz *et al*, 2020	Integration of the ImageJ system in the KNIME analytics platform was used in single-cell analysis of AR^+ LNCaP cells, which could be used to test future therapeutic agents targeting the AR pathway and AR activation in PCa.	H&E, Gene profiling	PCa	DA & DB	(100)
Bulten *et al*, 2020	A newly developed DL system was introduced to delineate individual glands, assign Gleason growth patterns and determine the biopsy-level grade in H&E stained WSIs from prostate biopsies, with a similar performance to pathologists.	H&E	PCa	DA	(101)
Han *et al*, 2020	A total of seven ML techniques were applied to detect and grade PCa based on H&E stained WSIs.	H&E	PCa	DB	(102)
Cascianelli *et al*, 2020	A strategy, named AWCA, was proposed to be integrated with PAM50, which could be applied as a single-sample method to improve classification robustness with high concordance and prognostic ability in BC. A total of five supervised learners were explored to build robust, single-sample intrinsic subtype callers via RNA-seq, which regularized mLR and displayed the best performance with classifications, robustness and prognostic ability, resulting in strengthening BC subtyping.	Gene profiling	BC	DA	(33)
Yu *et al*, 2020	A GO enrichment based on gene co-expression networks (GOEGCN) was proposed to study how the modulated	Gene profiling	BC	DA	(34)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
	co-expressed gene couples impacted biological functions at a GO level among all the BC subtypes, to some extent.				
Valle *et al*, 2020	A topic modeling was proposed to analyze TCGA transcriptomic data from BC and LC to reconstruct cancer subtypes and predict prognosis.	Gene profiling	BC&LC	DA & CP	(35)
Jaber *et al*, 2020	A DL approach for approximating PAM-50 intrinsic subtyping was developed using only H&E stained WSIs of breast biopsy tissue sections.	H&E	BC	DA	(103)
Valieris *et al*, 2020	An efficient ML algorithm was used to predict DRD from H&E stained WSIs.	H&E	BC and GC	DB & DPr	(104)
Woerl *et al*, 2020	DL was applied to predict the molecular subtype of MIBC samples from H&E stained WSIs.	H&E	MIBC	DA	(17)
Chen *et al*, 2020	scRNA-seq was used to understand the TME of NPC for developing targeted therapy and predicting patient prognosis.	Gene profiling	NPC	CP & DB	(37)
Zhou *et al*, 2020	scRNA-seq was used to detect intra-tumor heterogeneity and TIME in advanced OS.	Gene profiling	OS	DB	(38)
Kong *et al*, 2020	An ML framework was observed to predict drug response in patients with CRC or BLCA by using organoid model-derived drug genome data.	Gene profiling	CRC and BLCA	DB & CP	(40)
Skrede *et al*, 2020	A total of 10 CNNs, proposed for classifying supersized heterogeneous images, were used to predict patient outcomes by analyzing a prognostic biomarker in CRC H&E stained WSIs.	H&E	CRC	CP	(105)
Reichling *et al*, 2020	Software was developed to detect colon tumor, healthy mucosa, stroma and immune cells on CD3 and CD8 stained slides to automatically quantify the lymphocyte density and surface area of the tumor core and invasive margin. Digital parameters within the tumor cells related to patient outcomes were analyzed using a LASSO algorithm, DGMate (DiGital tuMor pArameTErs). The results suggested that AI could potentially improve patient care by assisting pathologists in better defining the prognosis of patients with stage III colon cancer.	H&E, IHC	CRC	CP	(106)
Bao *et al*, 2020	A validated AI-assisted cytology system was used to conduct a perspective cohort study within a population-based CC screening program for	PAP	CC	DA & DPr	(107)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
	0.7 million women, with the results supporting the AI-based cytology system for primary CC screening in large-scale populations.				
Xu-Monette *et al*, 2020	An NGS-COO model was built to classify DLBCL from genetic and transcriptional data obtained by RNA-seq with a similar performance to COO classification by either Affymetrix GeneChip microarray or the NanoString Lymph2Cx assay. Moreover, the NGS survival models were shown to stratify 30% high-risk patients with poor prognosis.	Gene profiling	DLBCL	DA & CP	(108)
Foersch *et al*, 2021	DL was used to accurately diagnose frequent subtypes of STS using H&E stained WSIs.	H&E	STS	DA	(109)
Lagree *et al*, 2021	A CAD pipeline using AI was introduced to assess the biomarkers for grading tumors in BC.	H&E, IHC	BC	DA	(110)
Bychkov *et al*, 2021	ML algorithms were used not only to predict the amplification of *ERBB2* based on tumor morphological features from TMA, but also to predict the survival and efficacy of anti-ERBB2 treatment.	H&E, CISH, v	BC	DB & CP	(111)
Li *et al*, 2021	A novel DL-based biomarker that predicted pCR from images of H&E stained WSIs was proposed and its predictive performance in BC was evaluated, resulting in a superior performance compared with other conventional biomarkers including sTILs and tumor subtype.	H&E	BC	DB	(112)
Chakraborty *et al*, 2021	XAI models were used to retrieve immune cell composition estimates from bulk RNA-seq data from TCGA breast invasive carcinoma data from the cbioPortal compared with TIMER2.0 based on EPIC, CIBERSORT, TIMER and xCell computational methods. Novel insights derived from the XAI model showed that B cells, $CD8^+$ T cells, M0 macrophage, and NK T cells are the most critical TME features for enhanced prognosis of patients with BC.	Gene profiling	BC	CP	(113)
Fitzgerald *et al*, 2021	DL platforms for capturing information from the image characteristics of H&E images could offer new possibilities for better modelling of disease appearance	H&E	BC and PCa	DA, CP & DB	(114)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
	and possibly improve the prediction of disease stage and patient outcomes.				
Ayyad *et al*, 2021	CAD systems were applied to aid in the diagnosis of PCa by capturing information from WSIs.	H&E	PCa	DA	(115)
Haggenmüller *et al*, 2021	A total of 19 readers, including 11CNN-based approaches addressing the classification of dermoscopic images, six concentrating on the classification of clinical images, and two utilized for WSIs, were used to classify tumors and assess their potential clinical relevance in melanoma, with a superior or at least equivalent performance compared with human experts.	H&E	Melanoma	DA & CP	(116)
Kiehl *et al*, 2021	A CNN-based image analysis could help predict LNM of patients with CRC using H&E stained WSIs.	H&E	CRC	DA & CP	(117)
Yamashita *et al*, 2021	A DL model (MSINet) was developed to predict MSI on H&E stained WSIs of CRC, which showed exceeded performance.	H&E	CRC	DA & DB	(118)
Krause *et al*, 2021	A 'histology CGAN' was proposed to detect genetic alterations (MSI) from routine histology images in CRC.	H&E	CRC	DA & DB	(119)
Cancian *et al*, 2021	A DL pipeline based on the DeepLab-v3 architecture and semantic segmentation technique warranted the separation of TAMs from the background and the identification of single TAMs on H&E stained WSIs from CRC liver metastasis	H&E	CRC liver metastasis	CP & DB	(24)
Bian *et al*, 2021	A DL-based computational framework (ImmunoAIzer) was proposed to characterize cell distribution and gene mutations in the TME of CRC.	H&E, IHC	CRC	CP & DB	(25)
Saito *et al*, 2021	An ML-based SVM was proposed to predict the early recurrence of HCC after resection from H&E stained WSIs.	H&E	HCC	CP	(120)
Yamashita *et al*, 2021	A DL-based system (HCC-SurvNet) provided recurrence risk scores, which might augment current patient stratification methods and help refine the clinical management of patients undergoing primary surgical resection for HCC.	H&E	HCC	DA/ DB	(121)
Yang *et al*, 2021	The first DL-based six-type classifier for histopathological WSI classification of LUAD, LUSC, SCLC, pulmonary tuberculosis, organizing pneumonia and normal lung was developed with a similar performance to experienced pathologists, and superior performance to other existing computational methods.	H&E	LC	DA	(122)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Chen *et al*, 2021	A method based on training neural networks on entire WSIs using only slide-level diagnostics was applied to classify LC subtypes.	H&E	LC	DA	(123)
Park *et al*, 2021	An algorithm based on CNN was observed to classify WSI-based gastric biopsies into three diagnostic categories (NFD, TA or carcinoma) with an outperformance.		GC	DA	(124)
Wang *et al*, 2021	Total WSIs of lymph nodes were analyzed using a DL framework to identify lymph nodes and tumor regions, and then assess the ratio of tumor area to LNM area with a similar performance to experienced pathologists.	H&E	GC	CP	(125)
Muti *et al*, 2021	A DL-based classifier was developed and validated to detect MSI and EBV status from H&E stained WSIs of GC.	H&E	GC	DB	(126)
Yan *et al*, 2021	A DTI-derived DLS was proposed to improve prediction accuracy of overall survival in patients with invasive glioma and classification accuracy of risk groups with distinct molecular pathway activities.	Gene profiling	Glioma	CP & DB	(127)
Bao *et al*, 2022	A robust ML model, an integrated stacking ML approach, was used for the early detection of the most prevalent and lethal cancer types using multiple plasma cfDNA fragmentomic features.	Gene profiling	HCC, CRC and LUAD	DPr	(128)
Duchmann *et al*, 2022	A mechanistic learning framework was used to predict the response to chemotherapy using dysplastic features and the oncogenetics of patients with AML treated in ALFA clinical trials.	Bone marrow smears, gene profiling	AML	CP & DB	(129)
Gimeno *et al*, 2022	A novel XAI method (MOM) was applied to an AML cohort of 319 *ex vivo* tumor samples with 122 screened drugs and whole-exome suquencing for guaranteeing that predictions were interpretable and robust. The predictive performance of MOM was successfully validated in three different large-scale screening experiments with a therapeutic strategy based on the FLT3, CBFβ-MYH11 and NRAS status, which predicted patient response to quizartinib, trametinib, selumetinib and crizotinib.	Gene profiling	AML	DB	(49)
Yen *et al*, 2022	Cox proportional hazard analysis was performed, and ML algorithms were applied to generate multivariate	IHC, gene profiling	CML	DB & CP	(130)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
	miRNA panels to predict nilotinib response at treatment-naïve or post-treatment time points. A combination of miR-145 and miR-708 were observed to be effective predictors of NL response in treatment-naïve patients, whereas miR-150 and miR-185 were significant classifiers at 1-month and 3-month post-NL therapy.				
Laukhtina *et al*, 2022	An ML-based variable selection method (LASSO regression) was used to determine the prognostic value with a set of preoperative SIR-biomarkers relative to standard clinicopathological variables to improve the selection of patients with mRCC for cell-reducing nephrectomy.	H&E	RCC	CP & DPr	(131)
Cheng *et al*, 2022	A total of four DNNs (ResNet50, InceptionV3, Xception and Ensemble) were introduced to improve diagnostic accuracy using H&E stained WSIs from patients with HNLs.	H&E	HCC	DA	(132)
Kleppe *et al*, 2022	A clinical decision support system based on the combination of DoMore-v1-CRC and pathological staging markers was developed to facilitate individualized choice of adjuvant therapy.	H&E	CRC	DA & DB	(133)
Byeon *et al*, 2022	A DL model was developed to automatically classify digital pathology images of colon lesions obtained from colonoscopy-related specimen with excellent performances for discriminating adenocarcinoma from non-adenocarcinoma lesions.	H&E	CRC	DA	(134)
Schrammen *et al*, 2022	SLAM was proposed to simultaneously detect tumor and predict genetic alterations from H&E stained WSIs.	H&E	CRC	DA& DB	(18)
Feng *et al*, 2022	An AI radiopathomics integrated model (RAPIDS) was proposed and validated to predict pCR in patients with locally advanced CRC using pretreatment MRI and H&E stained WSIs, which demonstrated an outperformance.	H&E, MRI	CRC	CP	(135)
Ding *et al*, 2022	A graph neural network approach was proposed to predict the comprehensive evaluation cross-level molecular profiles of genetic mutations, copy number alterations and functional protein expression from WSIs with favorable results.	H&E	CRC	DA & CP	(136)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Wang *et al*, 2022	A nomogram model combining ML pathomics, radiomics features, Immunoscore and clinical factors was constructed to predict the postoperative outcome of patients with CRC with lung metastasis, which demonstrated an outperformance.	H&E, MRI, IHC	CRC lung metastasis	CP	(137)
Sundar *et al*, 2022	A random forest ML model was applied on NanoString profiles to identify a gene signature to select patient benefits from paclitaxel treatment.	Gene profiling	GC	DB	(138)
Pfob *et al*, 2022	The feasibility of an ML algorithm (intelligent VAB) to identify exceptional responders to NST was evaluated in patients with BC with a favorable result.	H&E	BC	DB & CP	(139)
Prat *et al*, 2022	A supervised learning algorithm, HER2DX, was used to predict pCR and survival outcome from the gene profiling of early-stage HER2$^+$ BC, with an outperformance.	Gene profiling	BC	CP	(140)
Farinella *et al*, 2022	A DSS developed by an ML-based pipeline was applied to analyze an open-source HGSOC proteomic dataset, and it displayed high discerning ability on a dataset of HGSOC biopsies with the resulting output consisting of a combination of three highly discriminating proteins (TOP1, PDIA4 and OGN), which could be of interest for further clinical and experimental validation.	Gene profiling	HGSOC	DB	(141)
Meena and Hasija 2022	The XGBoost ML models (applications of XAI) were trained on binary classification datasets comprising expression data of 40 SCC, 38 AK and 46 normal healthy skin samples, resulting in 23 significant genes being identified and found to be associated with the progression of SCC.	Gene profiling	SCC of the skin	DA & CP	(50)
Park *et al*, 2022	An AI-powered WSI analyzer of TILs in the TMA that could define three immune phenotypes (inflamed, immune-excluded and immune-desert) was proposed, with an outperformance.	H&E, TMA	LC	DA, CP & DB	(142)
Cheng *et al*, 2022	A DL-based AI model was developed to automatically analyze the IHC expression of PD-L1 in patients with LC, with a similar performance to pathologists.	IHC	LC	DA & DB	(143)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Vanguri *et al*, 2022	An ML-based multimodal model was developed to predict immunotherapy response to PD-L1 blockade by capturing the integrated information of medical imaging, histopathologic and genomic features as well as the clinical data from patients with advanced NSCLC.	H&E, IHC, gene profiling	LC	CP & DB	(144)
Liu *et al*, 2022	A novel processing pipeline for nuclear segmentation, cell-level image feature extraction, and patient-level feature aggregation was introduced to facilitate the evaluation of pathological prognosis in patients with neuroblastoma.	H&E	NB	CP	(145)
Altini *et al*, 2022	The performance of NDG-CAM in nuclei detection was demonstrated to be in-line with state-of-the-art methods in five datasets based on histopathology WSIs.	H&E	Five datasets, including BC	DA	(48)
Sorin *et al*, 2023	A highly multiplexed IMC was applied to characterize the cellular landscape of he LUAD TIME, which demonstrated an outperformance in patient prognosis analysis using multiplex immunofluorescence staining techniques to label immune cells in the TIME and combining it with AI.	Gene profiling	LUAD	CP & DB	(39)
Rakaee *et al*, 2023	An ML-based TIL scoring approach was developed to evaluate TILs associated with clinical outcomes in patients with advanced NSCLC who received anti-PD-L1 monotherapy. The result was the best evidence to date that TILs are closely associated with a benefit from ICI.	H&E	NSCLC	CP & DB	(22)
Foersch *et al*, 2023	A multi-stain DL model utilizing AI was applied to determine the AImmunoscore in >1,000 patients with CRC for the prediction of prognosis and therapy, with a favorable result.	H&E, IHC	CRC	CP & DB	(146)
Liu *et al*, 2023	An ML-based pipeline was introduced to identify the CMBs from the TCGA-LGG cohort and assess the association between CMS and the prognosis and treatment response in LGG, with an outperformance.	H&E	LGG	CP & DB	(147)
Cao *et al*, 2023	An unsupervised generative adversarial network was applied to validate ultraviolet-photoacoustic-microscopy images o allow for rapidly pathologic diagnoses of bone tissue and aid the intraoperative determination of tumor margins.	H&E, frozen sections	Bony sarcomas	DA	(148)

Table II. Continued.

First author/s, year	Characteristic	Staining	Tissue/cell	Task	(Refs.)
Wu *et al*, 2023	A lymph node metastases diagnostic mode was developed to assess the clinical effect of an AI-assisted workflow.	H&E	BLCA	DA	(149)

ADH, atypical ductal hyperplasia; AECOX, AutoEncoder with Cox regression network; AI, artificial intelligence;AML, acute myeloid leukemia; ANN, artificial neural network; BC, breast cancer; BCCs, basal cell carcinomas; BLCA, bladder cancer; BL, Burkitt lymphoma; CC, cervical cancer; CAD, computer-aided diagnostic; cfDNA, cell-free DNA; CISH, chromogenic in situ hybridization; CMBs, cellular morphometric biomarkers; CMS, cellular morphometric subtypes; CML, Chronic myeloid leukemia; CNN, convolutional neural network; CRC, colorectal cancer; DA, diagnostic accuracy; DB, drug benefit; DCNN, deep convolutional neural networks; DLBCL, diffuse large B-cell lymphoma; DLS, deep learning signature; DPr, disease prevention; DSS, decision support system; DTI, diffusion tensor imaging; CP, cancer prognostication; DCIS, ductal carcinoma in situ; DRD, DNA repair deficiency; EMaGACO, Expectation-maximization-driven geodesic active contour with overlap resolution; FCN, fully convolutional neural networks; FISH, fluorescence in-situ hybridization; FL, follicular lymphoma; GBM, glioblastoma multiforme; GC, gastric carcinoma; GO, gene ontology; GSC, genomic sequencing classifier; HCC, hepatocellular carcinoma; HGSOC, High-grade serous ovarian cancer; HNCA, head and neck carcinoma; HNLs, hepatocellular nodular lesions; IBL, intraductal breast lesions; ICC, immunocytochemistry; IHC, immunohistochemistry; LC, lung cancer; LGG, lower grade glioma; LNM, lymph node metastasis; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MIBC, muscle-invasive bladder cancer; miRNA, microRNA; miR, microRNA; ML, machine learning; mLR, multiclass logistic regression; MM, malignant mesothelioma; MOM, multi-dimensional module optimization; mRCC, metastatic renal cell carcinoma; MSI, microsatellite instability; NB, neuroblastoma; NEP, neighboring ensemble predictor; NFD, negative for dysplasia; NGS, next-generation sequencing; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; NST, neoadjuvant systemic treatment; OC, ovarian cancer; OHbIC, oral cavity histomorphometric-based image-classifier; OS, osteosarcoma; OSCC, oropharyngeal squamous cell carcinoma; PCa, prostate cancer; PAP, Papanicolau; pCR, pathological complete response; RNA-seq, RNA sequencing; SC-CNN, spatially constrained convolutional neural network; SCLC, small cell lung carcinoma; scRNA-seq, single cell RNA sequencing; SIMMS, Subnetwork Integration for Multi-Modal Signatures; SLAM, slide-level assessment model; SLNB, sentinel lymph node biopsy; SLL, small lymphocytic lymphoma; SSAE, stacked sparse autoencoder; SCC, squamous cell carcinoma; sTILs, stromal tumor-infiltrating lymphocytes; STS, soft tissue sarcomas; SVM, support-vector-machine; TA, tubular adenoma; TAMs, tumor-associated macrophages; TCGA, Cancer Genome Atlas; TILs, tumor-infiltrating lymphocytes; TIME, tumor immune microenvironment; TMA, tissue microarray; TME, tumor microenvironment; TNBC, triple-negative breast cancer; UC, urothelial carcinoma; UCEC, uterine corpus endometrial cancer; UDH, usual ductal hyperplasia; VAB, vacuum-assisted biopsy; wFDT, weighted fuzzy decision trees; WSIs, whole-slide images; XAI, explainable artificial intelligence.

Numerous studies have focused on the risk stratification for cancer, especially for the globally leading cause of cancer deaths, LC. For instance, Choi and Na (19) proposed a novel DL-based risk stratification model to predict prognosis for patients with LUAD based on a gene co-expression network, which exhibited a significant association with patient prognosis independent of other clinicopathological features. Moreover, Choi *et al* (20) designed a robust Genomic Sequencing Classifier (GSC; a second-generation risk stratification algorithm) based on whole transcriptome RNA sequencing to validate the gene expression values predicting clinicopathological features of several LC cohorts. Compared with the Bronchial Genomic Classifier (the first generation), the GSC presented an optimized risk stratification across several independent LC cohorts, which aided physicians in capturing the optimal actionable information for the precision medicine of patients.

Growing evidence has shown that the TME, which is a complex physical and biochemical system comprising tumor cells, tumor stromal cells, vascular cells, immune cells and cytokines, plays an important role in tumor initiation, progression, metastasis and drug resistance. One of the most notable advances facilitated by AI has been in the understanding of the tumor-infiltrating lymphocytes (TILs) of the TME. Based on information regarding the TME from multiple studies in which immune content response data from The Cancer Genome Atlas (TCGA) were comprehensively analyzed, Saltz *et al* (21) framed a comprehensive methodology (termed Computational Staining) based on CNNs to map TILs and analyze the molecular and clinical correlation of TILs from H&E-stained WSIs containing 13 TCGA cancer types (Table II). In the present study, TIL map structural patterns with competitive performance were generated and it was revealed that the TIL patterns were associated with tumor and immune molecular features, cancer type and patient survival, which laid a new milestone for TME research (Fig. 3). Rakaee *et al* (22) described an attempt to associate an ML-based assessment of TILs from standard histological images with the outcomes of anti-PD-L1 monotherapy in patients with advanced non-small cell LC (NSCLC), which provided evidence that AI-based patient TIL assessment may enhance precision therapy.

As another key component of the TME, tumor-associated macrophages (TAMs) were studied by Bao *et al* (23) in triple-negative BC through an integrated analysis of single-cell and bulk RNA-seq. A DL approach based on the neural network, PyTorch, for the TAM-related gene signature was observed to display high accuracy in predicting the immunotherapy response (Fig. 3). Moreover, Cancian *et al* (24) demonstrated that CNN-based DeepLab-v3 could accurately recognize TAMs from the background, and separate different TAMs in marked contrast to the other two CNN-based models, which may satisfy the requirements of clinical practice for the

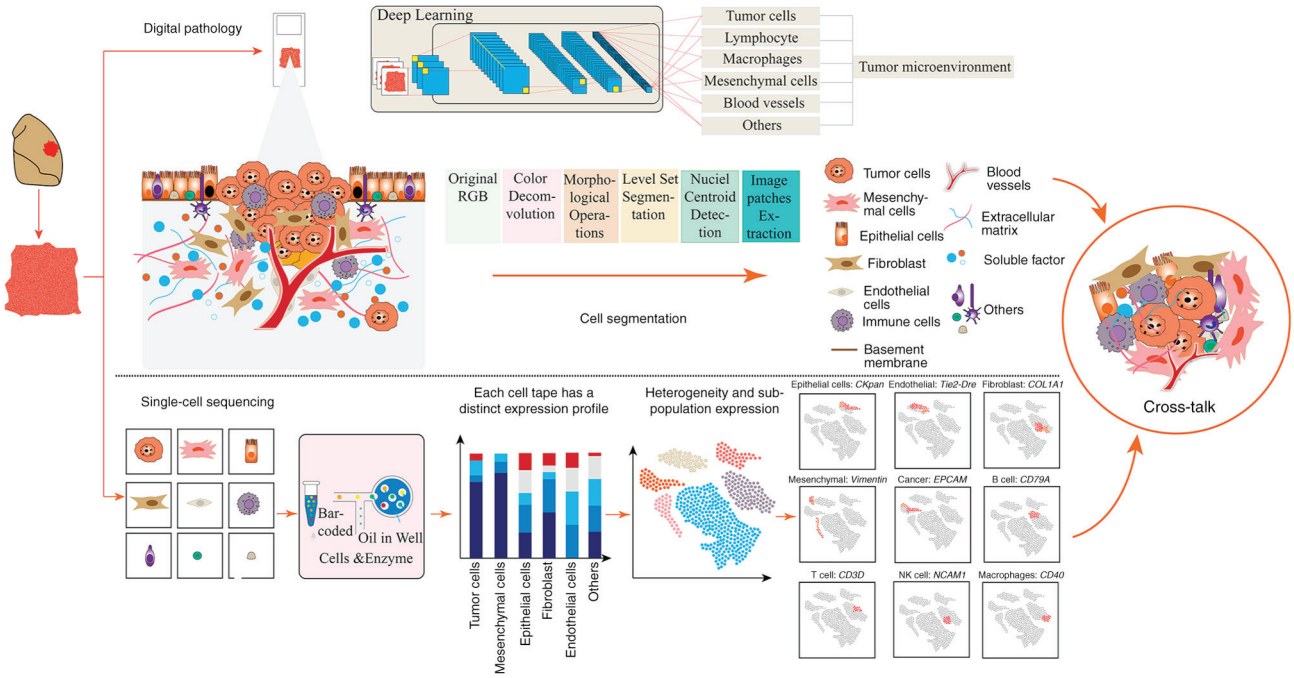

Figure 3. Overview of the AI-assisted analysis of the TME in cancer pathology. Current TME analysis approaches in AI-integrated cancer pathology generally rely on WSIs and gene profiling. Classically, numerous efforts have been devoted to capturing information about the TME from H&E, IHC or TMA based WSIs, such as H&E of 13 The Cancer Genome Atlas cancer types (21), H&E of BC (72), H&E and IHC of BC (71), IHC of BC (14), TMA of LC (142) and IHC of LC (90,143). Although these efforts have demonstrated an outperformance in the study of the TME, the platform of WSIs relying on images has limited the available information of TME for the AI-based approaches. Alternatively, with the emergence of cancer biomarkers and corresponding technologies, more foci from the TME from gene profiling by AI-based single cell RNA sequencing or next-generation sequencing have been reported, such as for BC (23,113), CRC liver metastasis (24,28), CRC (25), ovarian cancer (30), nasopharyngeal carcinoma (37) and osteosarcoma (38). These AI-based methods have provided new perspectives for research on the TME and made it prone to catching the information linked to the cross-talk between elements of the immune system with tumor cells in the TME. AI, artificial intelligence; BC, breast cancer; CRC, colorectal cancer; IHC, immunohistochemistry; LC, lung cancer; TMA, tissue microarray; TME, tumor microenvironment; WSIs, whole slide images.

characterization of TAM-related metrics in human colorectal liver metastases. In addition, Bian *et al* (25) designed a DL-based computational framework (termed ImmunoAIzer) to analyze the spatial distribution of immune cells and cancer cells in the TME and to detect gene mutations in colon cancer, which provided comprehensive information of cell distribution and tumor gene mutation status more efficiently and less expensively.

Moreover, tumor heterogeneity (including the contribution of the TME), an unneglectable factor affecting tumor evolution and therapy resistance, has also rapidly become a hot field of tumor phenotype research facilitated by AI. Undoubtedly, AI has made it easier to capture information from heterogeneous datasets to achieve accurate predictions and recognition patterns (26). For instance, since single-cell transcriptome sequencing technology was first reported by Tang *et al* (27) in 2009, and it has been widely applied in understanding molecular mechanisms and cellular properties of numerous biological processes, especially the tumor heterogeneity in various tumor types, such as CRC (28), ovarian cancer (29,30), head and neck cancer (31) and hepatocellular carcinoma (HCC) (32). In the light of this, Del Giudice *et al* (26) attempted to comprehensively review AI-based single-cell RNA-seq experiments in cancer from six network databases including the Genomic Data Commons Data Portal, ENCODE, Gene Expression Omnibus, Sequence Read Archive, Human Cell Atlas and Single Cell Portal, and sorted these experiments according to the tasks of AI models. These experiments, as well as the latest data, were categorized as defining cancer subtypes and cell clones (33-36), parsing tumor immune microenvironment (37-39), identifying new drug biomarkers (40), assessing and predicting disease recurrence and patient survival (41-45), detecting new putative actionable vulnerabilities (44,46) and predicting tumor immunoprofiling (47) (Table II) (26). More notably, the contributions of AI to the needs of cancer genomics for improving patient management were highlighted (26).

With the promise of continuing advances in the autonomous systems, explainable AI (XAI; the emerging generation of AI), which modified DL techniques to learn explainable features, has come to the fore in precision medicine, guaranteeing that predictions were more comprehensible and robust both in DP and MP. For example, Altini *et al* (48) tested the performance of NDG class activation mapping (NDG-CAM), a gradient-weighted CAM (one of the XAI applications) based method for nuclei detection in histopathology WSIs. NDG-CAM was observed to outperform in five datasets compared with other state-of-the-art methods. Moreover, Gimeno *et al* (49) developed a novel XAI method (multi-dimensional module optimization; MOM), which was applied to an acute myeloid leukemia (AML) cohort of 319 ex vivo tumor samples with 122 screened drugs and whole-exome sequencing. The predictive performance of MOM in AML was successfully validated in three different large-scale screening experiments with a therapeutic strategy

based on the *FLT3, CBFβ-MYH11* and *NRAS* status, which predicted patient response to quizartinib, trametinib, selumetinib and crizotinib (49). In addition, Meena and Hasija (50) described the outperformance of XGBoost ML models in identifying 23 significant genes of squamous cell cancer (SCC) of the skin, which may be the diagnostic and prognostic biomarkers of patients with SCC.

Taken together, AI has empowered MP by challenging itself, which mitigated various broken promises of precision medicine to improve the poor prognosis of different cancer types.

5. Application

To date, integration of AI and the cancer pathology workflow has achieved some breakthroughs for precision medicine, these applications were summarized and classified into four groups according to their principal tasks in precision medicine: DA, CP, drug benefit (DB) and disease prevention (DPr) (Figs. 1B and 2). A review of the literature from Google scholar and PubMed was conducted using the following terms: 'AI' AND 'pathology' AND 'cancer' AND 'diagnosis', or 'AI' AND 'pathology' AND 'cancer' AND 'therapy', or 'AI' AND 'pathology' AND 'cancer' AND 'prognosis'. or 'AI' AND 'pathology' AND 'cancer' AND 'prevention'. In total, ~20,000 available texts (Fig. 1B) were retrieved (most published studies had an impact factor of ≥5) and these principal applications of AI-integrated cancer pathology were listed chronologically for the first time (to the best of our knowledge) in Table II.

While reducing the workload of oncologists, the vast majority of these studies were concerned with integration of AI methods into cancer pathology to improve DA, including identification, classification, detection and discrimination of cancer and other malignancies. This means that integration of AI and cancer pathology has been used primarily as an aid to cancer diagnosis, and a great deal of effort has been devoted to address the bottlenecks in improving DA, such as low speed and efficiency of scanning slides, image distortion, spatial distribution complexities, limited recognition or auto-recognition ability and inefficient analytical capabilities, as well as the shortfalls for process integration (i.e., tradeoffs between performance and new features), etc. (Table II). Thus, these reasonable efforts have served to enhance the roles of cancer pathology in precision medicine, as far as possible, but they are not sufficient to keep pace with the ever-growing needs of personalized treatment.

Although the body of literature in the field of integration of AI into cancer pathology for CP is relatively small, the prediction of cancer prognosis has gained more attention, which is mainly attributed to the growth of MP. It is well-known that a cancer prognosis typically involves multiple physicians from different specialties using different subsets of biomarkers and multiple clinical factors, including the age and general health of the patient, the location, type, grade and size of the cancer, as well as the tumor-node-metastasis staging of the tumor. There are three predictive foci concerned with cancer prognostication, including the prediction of cancer susceptibility (i.e., risk assessment), the prediction of cancer recurrence and the prediction of cancer survivability. Differentiating these cancer predictive foci from biomarkers and factors may pose a problem. In this regard, as a consequence of the outperformance of AI integrated into MP driven by the rapid development of cancer biomarkers, which cover a broad range of biochemical entities, such as nucleic acids, proteins, sugars, small metabolites and cytogenetic and cytokinetic parameters, as well as entire tumor cells found in bodily fluids, improving predictions of prognosis via these biomarkers were observed in 10 types of TCGA cancer (41), soft tissue sarcomas (44), BC (46), cervical cancer (CC) (61), bladder cancer (73), glioma (82,127), AML (129) and chronic myelogenous leukemia (130) (Table II). Therefore, AI has helped clinicians to accurately stratify risk in patients via the assessment of various cancer biomarkers.

Similarly, encouraged by the emergence of cancer biomarkers and corresponding technologies, there has been a gradual increase in the studies related to the integrations of AI and cancer pathology in predicting drug benefits by evaluating novel cancer biomarkers, including *TIGIT* (38), activation of BH3-only proteins (39), amino acid synthesis and interconversion (39), tumor human leukocyte antigen peptide (47), *CTLA4* (66), oncotype DX and other gene expression (69), 21 genes (73), dysplasia (129), *TOP1*, *PDIA4* and *OGN* (141) (Table II). Accordingly, these studies have provided compelling evidence for the feasibility of developing targeted therapies against these molecules for patients to obtain optimized medical treatment.

Regardless of the number of papers focusing on DPr in terms of integration of AI and cancer pathology is the least among the four main tasks, the influence of these studies on cancer precision medicine remains vast. As a part of precision medicine, cancer prevention, which is generalized as being 'founded on describing the burden of cancer, identifying the causes, and evaluating and implementing preventive interventions', means there is 'a significant amount of work to be conducted'. Cancer prevention has achieved some success in reducing the global cancer incidence. The most convincing evidence is that tobacco control efforts and smoking cessation efforts as well as additional efforts, such as computed tomography for LC screening, since the 1960's will continue to reduce global LC incidence (150). Due to the advances in understanding cancer biology, precision prevention approaches have been made feasible in various types of cancer with the assistance of AI, such as in CRC (80,128), BC (91), CC (96,107), liver cancer (128), LUAD (128) and renal cell cancer (131) (Table II). It is hypothesized that these attempts will reduce global cancer burden in the future.

The integration of AI into these practices has allowed technologies to handle large amounts of data related to cancer pathology, which has not only alleviated the workload pressure of oncologists but has also improved the accuracy of diagnosis and prediction of cancer prognosis and drug benefits, as well as promoted DPr for precision medicine.

6. Discussion

At present, cancer remains a major public health problem worldwide, and cancer death was adversely affected by the coronavirus 2019 (COVID-19) global pandemic. Thus, there

is a pressing need to develop novel and effective strategies for cancer precision medicine. Although growing evidence indicates that a combination of cancer pathology and AI can bring exciting changes to cancer precision medicine, a large number of technical, ethical and legal challenges still need to be appropriately addressed.

Firstly, there are four main limitations in terms of technology level in the development of AI in cancer pathology, including: The quality and standardization of pathological images and WSIs (especially the images from 2D to 3D, if possible, or even 4D), the optimization of data, the interpretability of data and the verification of algorithms. Therefore, more efforts than could possibly be reviewed in the present review have been devoted to address these problems. For example, Zheng *et al* (151) created a Graph-Transformer fusing a graph-based representation of a WSI, and developed a graph-based digital pathology visual transducer to predict disease grade, which outperformed compared with current state-of-the-art methods for WSI classification. It is hypothesized that these behaviors could benefit cancer pathology ultimately with faster and more accurate diagnoses, as well as faster screening. Moreover, Qiao *et al* (152) described the rationalized DL-structured illumination microscopy and lattice light sheet microscopy system to build a minimally invasive 2D/3D live cell imaging system for following intracellular dynamics and trajectory, which provided the possibility that a novel system may be created in the future by extending the aforementioned capabilities to monitor the therapeutic effect of the treatments to tumor cells *in vivo* safely. In addition, owing to the fact that the effectiveness of these systems was limited by the inability of the machine to explain its thoughts and actions to human users, XAI, a suite of ML techniques, was created to promote safety and clarity by showing how decisions are made in AI models, especially in critical tasks, such as drug screening with genetic events (49,50) and drug-drug interaction predictions (153).

Nevertheless, cancer is a highly complex disease involving a cascade of microscopic and macroscopic changes with mechanisms and interactions that are not yet fully understood. With the continuous discovery of novel cancer biomarkers and the innovation of technologies, cancer biomarkers that provide insights into the state and course of disease in the form of quantitative or qualitative measurements have made the fusion of multiple medical perspectives to guide patient management feasible, which AI has promoted in multi-modal patterns. Since Chaudhary *et al* (83) first employed a DL-based model to identify multi-omics features to predict HCC survival risk, AI-guided research linked to multi-omics has emerged. For instance, Feng *et al* (135) proposed and evaluated an AI radiopath-omics integrated model (termed RAPIDS) to predict pathological complete response (pCR) to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer via pretreatment MRI and H&E stained WSIs. The results suggested that RAPIDS was able to predict pCR to neoadjuvant chemoradiotherapy, based on pretreatment radiopath-omics images, with high accuracy and robustness, which demonstrated a successful fusion of imagen-omics, path-omics and clinical data to predict patient prognosis (Fig. 4). Furthermore, Wang *et al* (137) built a nomogram model combining path-omics, radio-omics, protein-omics and clinical data to predict the postoperative outcome of patients with CRC and lung metastasis, which demonstrated an outperformance in risk prediction. Moreover, Vanguri *et al* (144) recently developed an ML-based multimodal model to predict immunotherapy response to PD-L1 blockade by capturing the information through a combination of imagen-omics, path-omics, genomics and clinical data from patients with advanced NSCLC. The model provided a quantitative rationale for using AI-guided multimodal integration to improve prediction of the drug benefits and outcomes in patients with NSCLC. Hence, synergies of cancer pathology with other medical tools could provide more information to the clinic to make an accurate and rapid decision in personalized treatments for patients. However, the well-known failed implementation of AI in oncology (the IBM Watson program at MD Anderson) is a reminder that multiple deployment challenges must be overcome prior to the integration of a pathology AI system into a clinical work environment (154,155). It is hypothesized that exploring the potential advantages of multimodal integration of path-omics, genomics, imagen-omics, protein-omics, epigenomics and other omics, as well as clinical data to make appropriate management decisions and improve patient outcomes may be the most challenging issue of cancer precision medicine in the future.

Notably, recent attempts to verify the capability of ChatGPT in effecting precision medicine have been reported since ChatGPT was released at the end of 2022, as it was reasonable to assume that using larger language models to enhance relationships through better communication would have a beneficial impact on patients (156,157). Sinha *et al* (158) assessed the capability of ChatGPT in solving higher-order reasoning regarding pathology and found that ChatGPT may offer meaningful responses but also current limitations.

Secondly, the vulnerability of ethics in the development of AI in cancer pathology cannot be ignored. With the introduction of WSI scanners, slides (as high-resolution digital images) can be captured, stored and transmitted electronically, and oncologists can annotate and label images as part of their reports. When the images and reports are stored in the cloud, the process allows third parties to share the information and associated data for research or other purposes. Moreover, oncologists have an obligation to keep identifiable patient information confidential (except with expressed consent), however, we consider that more could be done to ensure patient privacy and data security in this process. For instance, Chauhan and Gullapalli (159) posed three key foundational principles of ethical AI in the context of cancer pathology: Transparency, accountability and governance, to guide future practice. This viewpoint is appreciated, and it deserves popularizing in the clinic.

Thirdly, it has been recognized that the adoption of a new technology cannot be accomplished without some changes to the human and social aspects of the organization. The lack of global standardization has prevented the reusing of AI-integrated cancer pathology data to meet the broad range of patient safety and quality reporting requirements, which has been attributed to the following potential factors: i) The standardization for storage and retrieval of medical images; ii) the high standards and regulations that surround the cancer

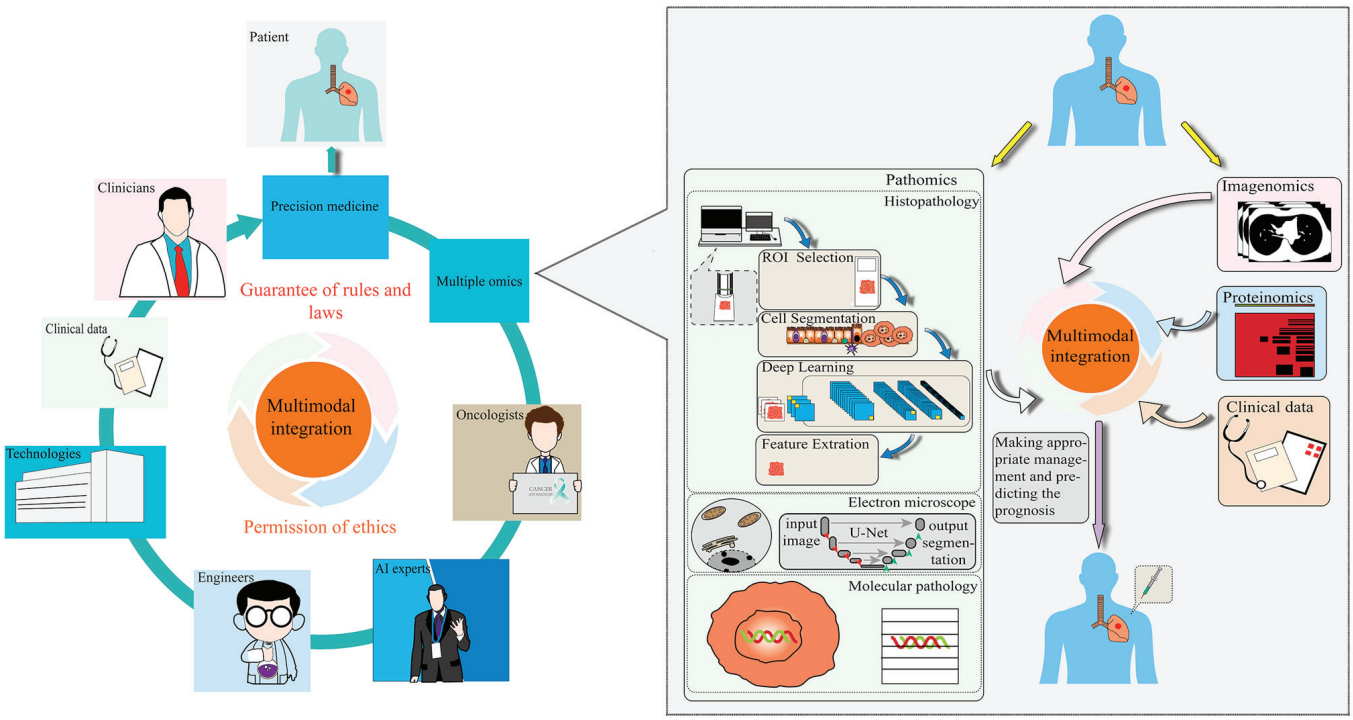

Figure 4. Multimodal integration of AI into precision medicine for patients with cancer. Since numerous issues stemming from the complexity of adopting AI in medical practice have been presented, multimodal features to improve the predictive capacity of AI-based medical approaches has successfully been applied in certain cancer types. For instance, the fusion of multi-omics and clinical data was used to determine an appropriate treatment management and predict the prognosis of patients with cancer, which was verified with outperformances in colorectal (135,137) and lung (144) cancer. However, there are still numerous challenges related to technology, ethics and the law of AI-based medical practice that need to be appropriately addressed. Thus, exploring the potential advantages of multimodal integration of multi-omics and clinical data to make appropriate treatment management decisions and improve patient outcomes may be the most challenging issue of cancer precision medicine in the future. AI, artificial intelligence.

pathology laboratory; iii) the adoption of a global diagnostic system (i.e., as with the World Health Organisation); iv) the normalization of validation systems; v) the establishment of corresponding legal liabilities related to AI; and vi) the oncologist, etc. To facilitate the integration of any medical data from any data owner worldwide without violating privacy laws, Warnat-Herresthal *et al* (160) proposed a decentralized ML approach termed Swarm Learning (SL), which united edge computing, blockchain-based peer-to-peer networking and coordination, while maintaining confidentiality without the need for a central coordinator, thereby going beyond federated learning. They chose four cases of heterogeneous diseases (COVID-19, tuberculosis, leukemia and lung pathologies) with >16,400 blood transcriptomes derived from 127 clinical studies with non-uniform distributions of cases and controls and substantial study biases, as well as >95,000 chest X-ray images to validate the feasibility of using SL to develop disease classifiers using distributed data. The results demonstrated that SL classifiers outperform those developed at individual sites, which allows for further study in more cancer types (160). It is hoped that in addition to establishing new rules and laws to provide a comprehensive guarantee for the development of AI in oncology pathology, more options could be explored to integrate the medical data for precision medicine to the extent allowed by laws (Fig. 4).

In conclusion, the 21st century has witnessed tremendous breakthroughs in AI and cancer pathology, and most of these creations and innovations have improved and advanced understanding of these systems. As such, it is hoped to improve understanding of the concepts related to these systems and to help others realize the goals of precision medicine.

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Authors' contributions

JP designed the review, wrote and revised the manuscript with input from BL, JF, QZ, QJ. BL, JF, QZ, ND, QJ and JP performed and analyzed the literature search. JF and BL made the figures. QZ, BL and JP completed the major part of tables. QJ participated in revising the review critically for

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Competing interests

The authors declare that they have no competing interests.

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