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AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

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Artificial intelligence in pathological evaluation of gastrointestinal cancers

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Abstract

The integration of artificial intelligence (AI) has shown promising benefits in many fields of diagnostic histopathology, including for gastrointestinal cancers (GCs), such as tumor identification, classification, and prognosis prediction. In parallel, recent evidence suggests that AI may help reduce the workload in gastrointestinal pathology by automatically detecting tumor tissues and evaluating prognostic parameters. In addition, AI seems to be an attractive tool for biomarker/genetic alteration prediction in GC, as it can contain a massive amount of information from visual data that is complex and partially understandable by pathologists. From this point of view, it is suggested that advances in AI could lead to revolutionary changes in many fields of pathology. Unfortunately, these findings do not exclude the possibility that there are still many hurdles to overcome before AI applications can be safely and effectively applied in actual pathology practice. These include a broad spectrum of challenges from needs identification to cost-effectiveness. Therefore, unlike other disciplines of medicine, no histopathology-based AI application, including in GC, has ever been approved either by a regulatory authority or approved for public reimbursement. The purpose of this review is to present data related to the applications of AI in pathology practice in GC and present the challenges that need to be overcome for their implementation.

Key Words: Digital image analysis; Digital pathology; Colorectal cancer; Gastric cancer; Machine learning; Deep learning

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Core Tip: Recently, based on improvements in efficient computational power and learning capacities, various artificial intelligence applications, such as image-based diagnosis and prognosis prediction, have emerged in many fields of pathology. This

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review comprehensively summarizes the current status of artificial intelligence applications in gastrointestinal cancers. The present data are promising for the use of artificial intelligence to diagnose tumors, evaluate prognostic parameters, and detect biomarker/genetic alterations. However, many challenges hinder the implication of artificial intelligence models in real pathological practice. Therefore, these challenges and suggested solutions are also briefly presented to improve the accuracy and relevance of artificial intelligence in pathological practice, including in gastrointestinal cancers.

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INTRODUCTION

Pathology is a medical specialty that performs morphological evaluations of organs, tissues, and cells to provide a definitive diagnosis of diseases and contributes to treatment by determining the critical parameters in their course[1]. Although histopathological assessment under a light microscope is considered a cornerstone, especially in oncology, the search for more objective criteria to overwhelm the subjectivity related to interobserver and intraobserver variations and to diminish the increased workload and time consumption has led to the development of image analysis-based digital pathology (DP), which plays a crucial role in modern pathological practice[2,3].

Following the considerable advances of slide scanner technology that can quickly digitalize whole pathological slides at high resolution (whole-slide images, WSI), in 2017, the approval of the Philips IntelliSite whole-slide scanner (Philips Electronics, Amsterdam, Netherlands) by the Food and Drug Administration (FDA) in the United States allowed a comprehensive evolution in DP[4]. This digitization not only facilitated the application of telepathology and created a valuable resource for education but also yielded the analysis of a large spectrum of morphological parameters and biomarkers/genetic alterations[5-7]. In addition, such digital images are constituted from matrices of numbers that contain much more information that is not accessible to the human eye[8,9]. Indeed, it may be possible to extract predictive and prognostic biomarkers from such digitized slides by computer-based image analysis. These methods are particularly of direct interest to "computational pathology", a relatively new pathology field driven by artificial intelligence (AI) that is expected to transform and improve the diagnosis and staging of cancers[3,10]. As a result, pathological AI models have evolved from expert systems to traditional machine learning (ML) and, finally, deep learning (DL)[11]. While the traditional supervised ML allows the production of data output from previously labeled training sets that can be corrected by the users, labeling big data can be time-consuming and challenging[12]. In addition, the accuracy depends heavily on the quality of feature extraction. In contrast, unsupervised ML is a time-saving model because it provides automatic detection of patterns[13]. However, input data that are not labeled by users pose challenges during interpretation, leading to varying results.

On the other hand, DL extracts features directly from the raw data and utilizes multiple layers of hidden data for the output[14-16]. Compared to expert systems and handcrafted ML models, DL models are simpler to conduct, have higher precision, and are more cost-effective[9,17] (Table 1). Furthermore, a considerable increase in computational processing capacity and the development of algorithms, such as convolutional neural networks (CNNs), fully CNNs, recurrent neural networks (RNNs), and generative adversarial networks, have resulted in numerous investigations on the application of DL-based AI in pathological practice[7,18,19]. The strengths and weaknesses of typical ML methods are summarized in Table 1.

In addition, the use of AI in pathology has led to the emergence of many DL-based applications[20]. Proscia, DeepLens, PathAI, and Inspirata are DL-based applications for the detection, diagnosis, and prognosis of several cancer subtypes[21-25]. In addition, Inspirata and PAIGE.AI are spending substantial time and resources on

Table 1 Strengths and weaknesses of machine learning methods in development of artificial intelligence models for gastrointestinal pathology

AI model	Advantages	Disadvantages
Traditional ML (supervised)	Allows users to produce a data output from the previously labeled training set Users can reflect domain knowledge features	Labeling big data can be time-consuming and challenging Accuracy depends heavily on the quality of feature extraction
Traditional ML (unsupervised)	Users do not label any data or supervise the model Can detect patterns automatically Save time	Input data is unknown and not labeled by users Users cannot get precise information regarding data sorting Challenges during interpreting
CNN	Detects the important information and features without labeling High performance in image recognition	A large training data is required Lack of interpretability (black boxes)
FCN	Provides computational speed Automatically eliminates the background noise	Requires large amounts of labeled data for training High labeling cost
RNN	Can decide which information to remember from its past experience A deep learning model for sequential data	Harder to train the model High computational cost
MIL	Does not require detailed annotation Can be applied to large data sets	A large amount of training data is required High computational cost
GAN	Generates new realistic data resembling the original data	Harder to train the model

AI: Artificial intelligence; ML: Machine learning; CNN: Convolutional neural networks; FCN: Fully convolutional neural networks; RNN: Recurrent neural networks; MIL: Multi-instance learning; GAN: Generative adversarial networks.

creating large libraries of digital WSI for use in training AI algorithms[21,24]. Interestingly, the landscape of DP is, in parallel, also undergoing important innovation and rapid changes[10].

It is also notable that some institutions are digitizing their entire pathology workflow, suggesting the routine use of AI-based systems in many areas of pathology soon[26,27]. Indeed, many studies have suggested that the integration of AI provides benefits for diagnosing and subtyping tumors, detecting histopathological parameters related to prognosis, and even identifying biomarker/genetic alterations in many fields of pathology[28]. On the other hand, the existence of a broad spectrum of difficulties, from AI-based pathology laboratory infrastructures to the robustness of algorithms, indicates that there are still many obstacles to be resolved before introducing AI applications in real-life pathology practice[29]. Nonetheless, AI-based approaches have the potential to contribute to pathological practice by improving workflows, eliminating simple errors, and increasing diagnostic reproducibility.

Regarding the gastrointestinal system, the accumulated data indicate that AI-based models might provide diagnostic assistance, prognosis prediction, and biomarker development for gastrointestinal cancer (GC). There have been few studies in the recent past that have addressed the effectiveness of AI models in GC[8,30]. However, effective implementation of these methods in real-life pathology practice requires further reviews comparing the results of previous studies and highlighting the challenges to be overcome.

This review presents recent data about the AI-based pathological evaluation of GC and current challenges for its implementation in gastrointestinal pathology practice with future directions to consider.

AI-BASED APPLICATIONS IN DIAGNOSIS OF GC

Recent studies on the use of AI models in the histopathological classification of gastric cancer are summarized in Table 2. Although the models used differ among studies, the results support that AI-based classification can be used in histopathological

Table 2 Artificial intelligence-based applications in gastric cancer

Ref.	Task	No. of cases/data set	Method	Performance
Duraipandian <i>et al</i> [89]	Classification	700 slides	GastricNet	Accuracy (100%)
Cosatto <i>et al</i> [72]		> 12000 WSIs	MIL	AUC (0.96)
Sharma <i>et al</i> [31]		454 cases	CNN	Accuracy (69%)
Qu <i>et al</i> [90]		9720 images	DL	AUCs (up to 0.97)
Yoshida <i>et al</i> [32]		3062 gastric biopsies	ML	Overall concordance rate (55.6%)
León <i>et al</i> [91]		40 images	CNN	Accuracy (up to 89.7%)
Liang <i>et al</i> [92]		1900 images	DL	Accuracy (91.1%)
Sun <i>et al</i> [93]		500 images	DL	Accuracy (91.6%)
Tomita <i>et al</i> [94]		502 images ¹	Attention-based DL	Accuracy (83%)
Wang <i>et al</i> [95]		608 images	Recalibrated multi-instance-DL	Accuracy (86.5%)
Iizuka <i>et al</i> [33]	Prognosis	1746 biopsy WSIs	CNN, RNN	Accuracy (95.6%), AUCs (up to 0.98)
Bollschweiler <i>et al</i> [41]		135 cases	ANN	Accuracy (93%)
Hensler <i>et al</i> [42]		4302 cases	QUEEN technique	Accuracy (72.73%)
Jagric <i>et al</i> [43]		213 cases	Learning vector quantization NN	Sensitivity (71%), specificity (96.1%)
Lu <i>et al</i> [36]		939 cases	MMHG	Accuracy (69.28%)
Jiang <i>et al</i> [37]		786 cases	SVM classifier	AUCs (up to 0.83)
Liu <i>et al</i> [40]		432 tissue samples	SVM classifier	Accuracy (up to 94.19%)
Korhani Kangi and Bahrapour[38]		339 cases	ANN, BNN	Sensitivity (88.2% for ANN, 90.3% for BNN) Specificity (95.4% for ANN, 90.9% for BNN)
Zhang <i>et al</i> [39]		669 cases	ML	AUCs (up to 0.831)
García <i>et al</i> [44]	Tumor infiltrating lymphocytes	3257 images	CNN	Accuracy (96.9%)
Kather <i>et al</i> [56]	Genetic alterations	1147 cases ²	Deep residual learning	AUC (0.81 for gastric cancer)
Kather <i>et al</i> [47]		> 1000 cases ³	NN	AUC (up to 0.8)
Fu <i>et al</i> [57]		> 1000 cases ⁴	NN	Variable across tumors/ gene alterations. Strongest relations in whole genome duplications

¹Esophageal adenocarcinoma and Barrett's esophagus.²Gastric and colorectal cancers.³Gastric, colorectal, esophageal, and liver cancers.⁴Gastric, colorectal, and pancreatic cancers.

AI: Artificial intelligence; GastricNet: The deep learning framework; WSIs: Whole slide images; MIL: Multi-instance learning; AUC: Area under the curve; CNN: Convolutional neural networks; DL: Deep learning; ML: Machine learning; RNN: Recurrent neural networks; ANN: Artificial neural network; QUEEN technique: Quality assured engineering of feedforward neural networks with supervised learning; NN: Neural network; MMHG: Multimodal hypergraph learning framework; SVM: Support vector machine.

evaluations based on the accuracy and area under the curve (AUC) values determined. Different models are considered together in a few studies. For example, in a study where two DL-based methods were used to diagnose gastric cancer, the mean accuracy of both models was shown to be up to 89.7% [31]. In another study that compared the classification results of experienced pathologists with those of the ML-based program created by NEC Corporation, in gastric biopsy specimens, the agreement rate for biopsy specimens negative for neoplastic lesions was found to be as high as 90.6% [32]. More recently, Iizuka *et al* [33], who aimed to classify gastric biopsies as gastric adenocarcinoma, adenoma, or nonneoplastic mucosa by using AI algorithms based on CNNs and RNNs, revealed that the AUC for gastric adenocarcinoma classification was 0.9, supporting that AI-based models could be helpful in the diagnosis of gastric cancer. Although these results suggest that AI can be used to diagnose gastric

cancer, it is difficult to relate these data to performance comparisons alone. In research, parameters such as the size of the dataset, resolution of detection, multisite validation, the number of categories to be classified, and most importantly, the presence of lesions other than malignancies that require diagnosis are also critical variables. In particular, the latter could be a potential limitation of AI-based models in actual practice. Indeed, a gastric biopsy is evaluated not only for malignancy but also for lesions such as gastritis and metaplasia. Therefore, an AI model used only for malignancy screening in gastric pathology will not reduce the pathologist's workload, as other findings also need to be reviewed.

AI applications have also been developed to diagnose colorectal cancer (CRC), which may allow classification of lesions as normal, hyperplasia, adenoma, adenocarcinoma, and histological subtypes of polyps or adenocarcinomas (Table 3). In an elegant study, Korbar *et al*[34] observed that their AI models could classify five colorectal polyp types with a 93% accuracy. In another study, a created DL model was able to reclassify colorectal polyps in a manner comparable to those of the pathologist, even in datasets from other hospitals[35]. From this perspective, the results of most studies are encouraging for the use of AI models in the diagnosis of CRC. However, this does not exclude the fact that comparing the performance of those models reliably necessitates a common task using a standardized dataset with standardized annotations because each model is derived from different datasets with different explanations and is focused on different tasks in current studies.

AI-BASED APPLICATIONS FOR PROGNOSTICATION OF GC

Because gastric cancer has more complex and heterogeneous morphological features than CRC, most AI-based studies performed on these tumors focus on diagnosis rather than prognostication studies (Table 2). Nevertheless, there is some evidence showing that AI models can be helpful to evaluate histopathological parameters, such as differentiation and lymphovascular involvement, which are essential in determining the survival time[36-38], recurrence risk[39,40], metastasis[41-43], and, accordingly, treatment of gastric cancer. In the survival analysis, a higher predictive accuracy for overall survival and disease-free survival than the tumor-node-metastasis staging system defined by the American Joint Committee on Cancer by SVM application has been demonstrated[37]. In addition, this method can also be used to predict adjuvant chemotherapeutic benefits, which can facilitate individualized therapy. Another study combining the demographics, pathological indicators, and physiological characteristics of the study group found that a method using a new multimodal hypergraph learning framework to improve the accuracy of survival prediction outperformed random forests and SVM in survival prediction[36]. Furthermore, when the artificial neural network and Bayesian neural network (BNN) values were compared in survival estimation, it was shown that BNN was superior to the artificial neural network method[38].

The application of neural networks significantly improves the prediction of lymph node metastasis[41]. In addition, in a study to determine the microenvironment that can predict tumor behavior, García *et al*[44] observed that a CNN model could be used to detect tumor-infiltrating lymphocytes (accuracy, 96.9%). However, the number of these studies should be increased to draw a better conclusion about the application of AI-based DP in the prognostication of gastric cancer.

In CRC, DL was found to be effective in predicting prognosis at all stages. For example, in a study where RNN analyzed tissue microarrays to predict 5-year disease-specific survival, the hazard ratio and AUC were determined to be 2.3 and 0.69, respectively[45]. In another study, a 99% accuracy was observed in estimating the course of the disease using more than 1000 histological images collected from three institutions[46]. Finally, in comparing five separate DL networks using 934 cases, Kather *et al*[47] observed that the hazard ratio was 1.99 in determining overall survival. In studies investigating the microenvironment with AI-based models in these tumors, AUC values ranged from 0.91 to 0.99[47-49]. In another interesting study, Weis *et al*[50] pointed out that detecting tumor bud hot spots with CNN may influence determining tumor budding, which plays a role in determining tumor behavior. The characteristics of these studies are briefly presented in Table 3. Although this needs to be supported and standardized by further comparative studies, all these findings suggest that AI can be applied for determining the behavior of CRC.

Table 3 Artificial intelligence-based applications in colorectal cancer

Ref.	Task	No. of cases/data set	Method	Performance
Xu <i>et al</i> [96]	Classification	717 patches (N, ADC subtypes)	AlexNet	Accuracy (97.5%)
Awan <i>et al</i> [97]		454 cases (N, ADC grades LG <i>vs</i> HG)	NN	Accuracy (97%, for 2-class; 91%, for 3-class)
Haj-Hassan <i>et al</i> [98]		30 multispectral image patches (N, AD, ADC)	CNN	Accuracy (99.2%)
Kainz <i>et al</i> [99]		165 images (benign <i>vs</i> malignant)	CNN (LeNet-5)	Accuracy (95%-98%)
Korbar <i>et al</i> [34]		697 cases (N, AD subtypes)	ResNet	Accuracy (93.0%)
Yoshida <i>et al</i> [100]		1328 colorectal biopsy WSIs	ML	Accuracy (90.1% for adenoma)
Wei <i>et al</i> [35]		326 slides (training), 25 slides (validation) 157 slides (internal set)	ResNet	157 slides: Accuracy 93.5% <i>vs</i> 91.4%(pathologists) 238 slides: Accuracy 87.0% <i>vs</i> 86.6%(pathologists)
Ponzio <i>et al</i> [101]		27 WSIs (13500 patches) (N, AD, ADC)	VGG16	Accuracy (96%)
Kather <i>et al</i> [47]		94 WSIs ¹	ResNet18	AUC (> 0.99)
Yoon <i>et al</i> [102]		57 WSIs (10280 patches)	VGG	Accuracy (93.5%)
Iizuka <i>et al</i> [33]		4036 WSIs (N, AD, ADC)	CNN/RNN	AUCs (0.96, ADC; 0.99, AD)
Sena <i>et al</i> [103]		393 WSIs (12565 patches) (N, HP, AD, ADC)	CNN	Accuracy (80%)
Bychkov <i>et al</i> [45]	Prognosis	420 cases	RNN	HR of 2.3, AUC (0.69)
Kather <i>et al</i> [46]		1296 WSIs	VGG19	Accuracy (94%-99%)
Kather <i>et al</i> [46]		934 cases	DL (comp. 5 networks)	HR for overall survival of 1.63-1.99
Geessink <i>et al</i> [104]		129 cases	NN	HR of 2.04 for disease free survival
Skrede <i>et al</i> [105]		2022 cases	Neural networks with MIL	HR 3.04
Kather <i>et al</i> [47]	Genetic alterations	TCGA-DX (93408 patches) ¹ TCGA-KR (60894 patches)	ResNet18	AUC (0.77), TCGA-DXAUC (0.84), TCGA KR)
Echle <i>et al</i> [55]		8836 cases (MSI)	ShuffleNet DL	AUC (0.92-0.96 in two cohorts)
Kather <i>et al</i> [47]	Tumor microenvironment analysis	86 WSIs (100000) ¹	VGG19	Accuracy (94%-99%)
Shapcott <i>et al</i> [48]		853 patches and 142 TCGA images	CNN with a grid-based attention network	Accuracy (65-84% in two sets)
Swiderska-Chadaj <i>et al</i> [49]		28 WSIs	FCN/LSM/U-Net	Sensitivity (74.0%)
Alom <i>et al</i> [106]		21135 patches	DCRN/R2U-Net	Accuracy (91.9%)
Sirinukunwattana <i>et al</i> [107]	Molecular subtypes	1206 cases	NN with domain-adversarial learning	AUC (0.84-0.95 in the two validation sets)
Weis <i>et al</i> [50]	Tumor budding	401 cases	CNN	Correlation R (0.86)

¹Gastric, colorectal, esophageal, and liver cancers.

AI: Artificial intelligence; N: Normal; ADC: Adenocarcinoma; LG: Low grade; HG: High grade; NN: Neural networks; AD: Adenoma; CNN: Convolutional neural networks; WSIs: Whole slide images; ML: Machine learning; VGG: Visual geometry group; AUC: Area under the curve; RNN: Recurrent neural networks; HR: Hazard ratio; DL: Deep learning; MIL: Multi-instance learning; TCGA: The cancer genome Atlas; MSI: Microsatellite instability; FCN: Fully convolutional neural networks; LSM: Locally sensitive method; DCRN: Densely connected recurrent convolutional network; R2U-Net: Recurrent residual U-Net.

AI-BASED APPLICATIONS FOR GENETIC AND MOLECULAR TESTING IN GC

In routine practice, evaluating surgical and biopsy specimens of GI cancers is essential

for identifying molecular biomarkers that predict the response to targeted therapies. This evaluation requires the use of immunohistochemistry or advanced molecular techniques.

The detection of genetic alterations called microsatellite instability (MSI), especially in CRC, is very important for treatment with immunomodulators[51-53]. In addition, it is possible to determine the MSI-related phenotype and identify conditions that require family information and close follow-up of the patient, such as Lynch syndrome [54]. The revelation that some of the genetic events in these cancers are associated with certain morphological events has led to several attempts to use AI-based algorithms in WSIs. Furthermore, due to the large number of samples available, CRC was seen as a prototype for these studies. In this context, accumulated data indicate that AI-based models are influential in determining both MSI and other genotypic changes[47,55-57]. In particular, the DL algorithm developed by Echle *et al*[55] to detect MSI in CRC using more than 8800 images recently showed an AUC of 0.96 in the multi-institution validation cohort (Table 3).

There have been other attempts to develop models that directly predict gene mutations from the WSI of gastric cancer. In addition, it has been observed that AI could also predict gene expression and RNA-seq data, and these models have remarkable potential for clinical translation[47,56,57] (Table 2).

However, further additional and prospective validation studies are necessary for GI cancers before applying AI in real life to reduce the molecular testing workload and allow testing in health care centers with limited resources.

CHALLENGES AND IMPLEMENTATION OF AI-BASED APPLICATIONS IN REAL-LIFE PRACTICE

In general, the need for a close review of the steps involved in ethics, design, financing, development, validation and regulation, implementation, and impact on the workforce in the application of AI in pathology has been highlighted[58].

From this perspective, although AI-based models are likely to play a critical role in gastrointestinal pathology, including GC, in the future, several problems similar to those in other fields of pathology need to be addressed to ensure implementation. Brief information about the difficulties encountered in applying AI models in pathology, including GC, and suggested solutions are presented in Table 4.

Ethical considerations

Although consent can be obtained from patients to use data for research purposes, a lack of approval for commercial use can cause problems in developing AI models[59]. Some researchers argue that this can be resolved by developing a framework for global data sharing by obtaining approvals that convey the possibility of commercial use for research and product development[30].

Design of AI models

The primary expectation of AI in pathology is to fill gaps and address unmet needs in the daily workflow. These needs mainly include workload-intensive and repetitive procedures, such as calculating tumor necrosis, mitotic count, and lymph node metastases, and diagnosing lesions prone to interobserver variabilities. The main goal to consider in developing AI applications in pathology is to solve a real clinical need. However, the development of models for AI application in this field of medicine involves a variety of stakeholders, including not just pathologists but computer scientists, IT, and pharmaceutical companies, which inevitably leads to different expectations and perspectives. For example, some may have academic publishing purposes, while others may be profitable commercial products. Therefore, an expected solution in pathology may not meet the expectations in finance, leading to the company not preferring to develop. To overcome these challenges and develop AI algorithms that are effectively used in DP, GC, pathologists, academic professionals who can develop technology, and companies that will promote the product must collaborate in harmony.

Development of AI models

Once AI models are designed and built, their development requires an accurate definition of the output, straightforward design of the algorithm, collection of a large follow-up sample or even pilot data, data disclosure and processing, and statistical

Table 4 Summary of challenges and suggested solutions in development process of artificial intelligence applications

Process	Challenges	Suggested solutions
Ethical considerations	Lack of patient's approval for commercial use	Approval for both research and product development
Design of AI models	Underestimation of end-users' needs	Collaboration with stake holders
Optimization of data-sets	CNN: Large amounts of images	Augmentation techniques, transfer learning
	Rare tumors: Limited number of images	Global data sharing
	Variations in preanalytical and analytical phases	AI algorithms to standardize staining, color properties, and WSIs quality
Annotation of data-sets	Interobserver variations in diagnosis	MIL algorithms
	Discrepancies among performances for trained algorithms	
Validation	Presence of ground truth without objectivity	Multicenter evaluations that include many pathologists and data-set
Regulation	Lack of current regulatory guidance specific for AI tools	New guidelines and regulations for safer and effective AI tools
Implementation	Changes in work-flow	Selection of AI applications that will speed up the work-flow
	IT infrastructure investment	Augmented microscopy directed to the cloud network service
	The relative inexperience of pathologists	Training about AI, integration of AI in medical education
	AI applications that lack interpretability (Black-box)	Constructions of interpretable models, generating attention heat map
	Lack of external quality assurance	Scheme for this purpose should be designed
	Legal implications	The performance of AI algorithms should be assured for reporting

CNN: Convolutional neural networks; MIL: Multi-instance learning.

analysis.

From this perspective, high-quality dataset optimization can be considered one of the biggest obstacles to the development of AI in DP. CNNs require a large number, even thousands, of pathological image datasets, to perform adequately[60]. Especially in rare tumors, the inability to obtain a very high number of images is quite limiting. To overcome this situation, the use of data augmentation techniques and learning methods is recommended. In contrast, Jones *et al*[61] indicated that small-scale datasets of < 100 digital slides might be sufficient in the case of transfer learning. Recently, it was proposed to develop publicly available datasets for global data sharing. However, it cannot be ruled out that very few such datasets are available in pathology, partially due to privacy, copyright, and financial issues[62]. Although The Cancer Genome Atlas provides many WSIs and associated molecular data, it does not contain enough cases for training AI applications for clinical practice[63,64]. Hartman *et al*[63] pointed out that another potential source of datasets could be public challenges provided for developing DL algorithms.

Again, developing high performance in AI applications in DP requires training on large datasets, which can be affected by the preanalytical (variations in fixation protocols and variations in the thickness of tissue sections) and analytical (variations in staining techniques and scanning protocols) phases applied to acquire digital images[65,66]. Indeed, converting a glass slide to WSI is not a simple task, and color modifications may influence the accuracy of AI. For this purpose, several AI algorithms have emerged to standardize data in recent years, including staining and color properties[67-69]. In addition, several automated algorithms have also been provided to standardize WSI quality, which automatically detects regions of optimum quality and removes out-of-focus or artifact-related regions, such as DeepFocus[70,71].

Annotation of the dataset

The curation of the dataset should be followed by annotation, which is another complex task. The limits of this annotation are broad, depending on AI, ranging from classification at the slide level to labeling at the pixel level[7,30]. For pathologists, the task of annotating many images is a time-consuming, sometimes challenging effort that can affect the accuracy of the models being trained, especially when the task is complex, especially if, as in gastrointestinal pathology, the disease selected for diagnosis differs significantly among observers (*e.g.*, intramucosal carcinomas) and if

the accuracy of dataset descriptions cannot be warranted[72]. Moreover, the trained algorithm may not produce the same performance in the dataset when used in other medical centers. Recently, many efforts have been made to solve the annotation problems that hinder the application of AI in pathology practice[67,73]. The data support that multi-instance learning (MIL) algorithms can be applied without detailed annotation. In particular, there is evidence that MIL can be effective when there is a large dataset and detailed annotations are impossible to obtain[60].

Validation and regulation

The preparation of the annotated dataset is followed by the model development process (preparation of the datasets for training, testing, and validation) and the selection of the learning method with the ML technique. In this context, the validation of AI-based technologies requires an evidence-based approach, and it is emphasized that analytical validation should also be considered in a laboratory-centered medical discipline, such as pathology^[58,73]. Therefore, it is essential to establish steps and criteria for validating new tests according to the standards. For example, to validate the image analysis used to determine the expression of a biomarker, the technique can often be compared to a detailed manual tumor assessment. However, the performance of the AI technique compared with that of pathologists is not straightforward, given the intraobserver and interobserver variability. Today, there are difficulties associated with determining "ground truth" to AI applications. This situation leads to the need for repeated validation of the robustness and reproducibility of AI applications in large and variable patient groups[30].

There may be a relative lack of validation cohorts in the development of AI-based applications in DP. This shortcoming is also contributed by the potential limitation in sharing histopathological sections. Although the interobserver variability and subjectivity in the evaluations of pathologists also indicate the uncertainty of "ground truth" in this aspect, the best measure to overcome this obstacle may be multicenter evaluations that include more than one pathologist and dataset. From the perspective of GC, the lack of external validation in a substantial number of studies for AI applications may limit the practical use of AI.

Regulation of AI

Although appropriate regulations are necessary for the safe and effective use of AI in pathology, as highlighted by Allen[74], regulatory approval should be structured to define the risk-benefit balance, reduce potential harm, produce appropriate verification standards, and encourage innovation. On the other hand, the presence of various challenges should not be ignored in this regard.

Various regulatory authorities [such as the FDA, Centers for Medicare and Medicaid Services (CMS), and the European Union Conformité Européenne (EUCE)] are not yet fully prepared for the implementation of AI applications in clinical medicine. As a result, AI-based devices are being controlled by old and potentially outdated guidelines for testing medical devices.

Currently, in the United States, the FDA is working on new regulations to make AI-based devices safer and more effective[75]. On the other hand, appropriate validation for all laboratory tests using human tissue prior to clinical application is required by CMS regardless of FDA approval, and this organization has no specific regulations to validate AI applications. Furthermore, the EUCE reported that *in vitro* diagnostic medical device directives will be replaced by *in vitro* diagnostic regulations in May 2022[76]. In addition, it is necessary to take into account the regulatory trends of the country where AI is implemented.

Implementation

The implementation of AI models in daily pathology practice depends on meeting specific requirements by overcoming various challenges. First, a laboratory infrastructure equipped to enable AI applications in a time frame that does not interfere with patient care is essential. Currently, many pathology laboratories only use tissue sections for diagnostic evaluations. However, the implementation of AI models will require new DP-related equipment, software, a specific data management system, data storage facilities, and, more importantly, a substantial investment to cover their cost[77]. In addition, an institutional IT platform is required to enable practitioners to operate on-site and cloud-based computing systems. Thus, DP applications may require significant investment, hindering the implementation of these technologies. It has been demonstrated that augmented microscopy directly connected to the cloud network service can solve the whole slide scanner setup problem[78]. The

cloud-based AI application developed by GOOGLE can also aid in the search for morphologically similar features in a target image, regardless of the annotation status [79].

The relative inexperience of pathologists with AI-based technologies should not be overlooked. Therefore, pathologists need to improve their knowledge of both the installation of DP systems and the application of AI. Another problem is that, given the reported performance of some algorithms, automated AI models are believed to outperform pathologists, causing pathologists to be hesitant about these applications [79-81]. However, current results suggest that AI models are more likely to help improve the overall quality of pathological diagnosis and provide relevant additional information rather than replacing pathologists [82,83]. Indeed, there will always be a need for pathologists to audit technologies and control systems in AI implementation. Therefore, pathologists must be aware of the long-term risk-benefit balance of AI applications [84]. Since current DL-based AI applications lack interpretability, it may be helpful to develop AI solutions that end-users can interpret, thus providing them with detailed explanations of how their predictions are made. Although DL's "black box" problem has not been fully resolved, several solutions have been reported, such as constructing an interpretable model, generating an attention heatmap, and constructing an external interpretive model [85-88].

While AI assistance in pathological diagnosis may reduce the opportunities for learning diagnostic skills during pathology training, resident pathologists should be trained and encouraged to learn the utility, limitations, and pitfalls of AI application as an adjunct method to improve the quality and precision of clinical diagnoses. Therefore, some reforms may be required in pathology training, starting with medical education followed by a pathology education program to address a more accurate and safer implementation of AI in pathology practice [84].

Like other clinical tests, quality assurance is an important issue for the effective use of AI in DP, and consequently, a scheme of external quality assurance for applications should be urgently prepared for its implementation. Furthermore, laboratory staff should be aware of the quality management system.

Beyond all this, the legal implications of signing a report prepared by a pathologist using AI should not be ignored. Therefore, to include AI findings in a pathological report, the performance of the algorithm must be assured. This legal issue also supports the notion that AI cannot replace pathologists but that AI can be used to support pathologists in clinical trials.

CONCLUSION

AI-based approaches have the potential to contribute to the pathological diagnosis and staging of GC by improving workflows, eliminating simple errors, and increasing diagnostic reproducibility. It is also the case that it encourages biomarker discovery by revealing impossible predictions using traditional visual methods. However, there are many hurdles to overcome, including infrastructure and the generalization of algorithms. Overcoming these obstacles requires the efforts of computer scientists, pathologists, and clinicians, who will deal with each challenge separately and cooperate in harmony. In this way, AI applications that are user-friendly, explainable, manageable, and cost-effective can play a crucial role in the development of pathological assessments to be used in the diagnosis, prognosis, and treatment of GC.

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