

Artificial Intelligence in *Gastroenterology*

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Artificial Intelligence in Gastroenterology

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The primary aim of *Artificial Intelligence in Gastroenterology* (AIG, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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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Implications of artificial intelligence in inflammatory bowel disease: Diagnosis, prognosis and treatment follow up

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Abstract

Driven by the tremendous availability of data, artificial intelligence (AI) using deep learning has emerged as a breakthrough computer technology in the last few decades and has recently been acknowledged by the Task Force on AI as a golden opportunity for research. With its ability to understand, learn from and build on non-linear relationships, AI aims to individualize medical care in an attempt to save time, cost, effort and improve patient's safety. AI has been applied in multiple medical fields with substantial progress made in gastroenterology mainly to facilitate accurate detection of pathology in different disease processes, among which inflammatory bowel disease (IBD) seems to drag significant attention, specifically by interpreting imaging studies, endoscopic images and videos and -to a lesser extent- disease genomics. Moreover, models have been built to predict IBD occurrence, flare ups, persistence of histological inflammation, disease-related structural abnormalities as well as disease remission. In this article, we will review the applications of AI in IBD in the present medical literature at multiple points of IBD timeline, starting from disease prediction *via* genomic assessment, diagnostic phase *via* interpretation of radiological studies and AI-assisted endoscopy, and the role of AI in the evaluation of therapy response and prognosis of IBD patients.

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Core Tip: There has been a substantial progress made in artificial intelligence in gastroenterology including inflammatory bowel disease. Machine learning would play a major role in predicting disease flare up, response to treatment and overall patient' prognosis.

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INTRODUCTION

Artificial intelligence (AI) refers to any technique by which the machine performs complex cognitive tasks similar to those of the human brain such as problem solving or learning. Machine learning (ML) is a subdivision of AI in which the machine automatically learns and improves without being explicitly programmed. Machine learning includes multiple techniques such as deep learning (DL), Bayesian inferences, support vector machines (SVM), artificial neural networks (ANNs), convolutional neural network (CNN) and others[1].

The intelligence of computing machinery was first described in the 1950[2], yet stayed dormant for few decades until the accumulation of large digital and clinical data and the evolution of computer systems which steered the wheel towards a more efficient utilization of available resources. At present, AI has been applied in multiple medical fields, including radiology, neurology, orthopedics, pathology, ophthalmology, in addition to the numerous applications in the field of gastroenterology including neoplastic and non-neoplastic disease processes such as infection, inflammation, and hemorrhage[3-6]. Yet it is not enough for the computer to only learn from the big dataset, this has to translate into meaningful clinical implications that will have positive outcomes in the way patients are being handled. Despite the novelty of this field, multiple applications stand there pointing to this clinical utility of AI. Taking inflammatory bowel disease (IBD) patients as an example, some of the algorithms that will be discussed later in this review had shown the potential ability of the computer to predict the histology by direct visualization of the mucosa. In an ideal world, this would mean that the AI algorithm can diagnose the patient while on the endoscopy table without the need for the invasive biopsy, and that physicians can immediately and more confidently start with treatment and any needed application for insurance companies rather than waiting for the biopsy result for days. In this example, AI demonstrates how can these algorithms save the patient and the clinician time to reach the diagnosis, improve patient's safety by omitting the need for biopsy, and improve the efficiency and workflow. To emphasize more on this point, the American Society for Gastrointestinal Endoscopy (ASGE) assembled the Task Force on AI that aims to direct research efforts toward AI implications that are expected to have more meaningful outcomes[7].

IBD, which is the main interest of this article, is a multifactorial disease of the gastrointestinal tract that results from complex interactions between various genetic, immune system, environment and microbiome-related factors. The non-linear relationships and interactions between the aforementioned factors-as with most living organism's phenomena-made the prediction of the disease onset, accurate diagnostic means, and customization of IBD treatment challenging tasks to achieve, presenting the application of the AI with its non-linear algorithms as a perfectly matching solution[8]. Furthermore, AI, and particularly DL, allows for maximum patient's stratification and optimal individualization of both diagnostic and therapeutic choices in addition to a tailored prognostic view, which positively affect the cost, health and safety.

Among other non-neoplastic processes, the application of AI in IBD seems to have dragged a significant attention especially in the last decade. The aim of this article is to review the applications of AI in the timeline of IBD; starting from the prediction of the disease onset, to diagnostic, therapeutic and finally follow up options.

AI AND IMAGES ANALYSIS

The diagnosis of IBD is a multistep process that matches disease's inherent complexity and multifactorial nature surrounded by a large number of confounding factors[8]. In clinical practice, IBD is diagnosed in an affected subject who is expressing compatible symptoms of either ulcerative colitis (UC) or Crohn's Disease (CD) in addition to a radiological, endoscopic and/or histological evidence of the corresponding inflammatory pattern. Despite the use of multiple scoring systems in an attempt to standardize the diagnostic efforts, the interpretation of any of these tests—and hence the final score—is still susceptible to a significant inter- and intra-observer variability, which only adds fog to the diagnostic horizon[9]. AI offers a great resource for human-independent interpretation and standardization, and has been increasingly recognized in the literature as a promising alternative for biopsy-guided diagnosis, severity determination, identification of remission and prediction of relapses. Multiple models have been developed and applied in different studies to explore this field mainly guided by the ability of the AI to interpret various radiological and laboratory data.

AI-guided interpretation of radiography

The current gold reference standard for diagnosing IBD is colonoscopy, which carries the risk of bowel perforation and procedure-related discomfort. Thus, looking for a different less invasive methods for diagnosis is justifiable and so is the application of AI. Computed tomography (CT) and magnetic resonance imaging (MRI) play a vital role in indicating the presence and extent of the disease, however; this comes at a time cost and more importantly-great subjectivity in the radiological interpretation. Despite the scarce literature in this field, the implementation of AI has shown its ability to standardize the interpretation process to better assess the extent of bowel involvement in a timely fashion with good results when compared to the manual interpretation (Table 1).

The presence of a structural bowel damage in IBD patients is a common cause for medical therapy failure, and early identification of such an entity is of a great value [10]. For this reason, Stidham *et al*[11] developed and validated a semi-automated model to identify strictures in CD patients. To validate the model, two expert radiologists retrospectively reviewed 138 CT-enterography scans for the presence of structural bowel abnormalities in previously known CD patients. The same scans then underwent semi-automated measurement analysis (maximum bowel thickness, maximum bowel dilatation minimum lumen diameter, and presence of stricture). The researchers found that the structural bowel damage measurements collected by the two expert radiologist were similarly comparable to those collected by the model, with no statistically significant difference between the average mean absolute measurements scored by the model compared to that between the two radiologists. The accuracy of radiologist-defined intestinal strictures using automated acquired measurements had an accuracy of 87.6%.

While the ultrasound and the CT use are generally limited by the gas interference and the exposure to the ionizing radiations, respectively; MRI has the ability to overcome both of these issues and the utilizations of AI-aided interpretation makes perfect sense. However, in contrast to the CT images which yield reproducible values, MRI images are greatly influenced by many other factors (ex: Signal fluctuations, heterogeneities in tissue) which complicate the processing of the data and limit the application of the automated techniques, and not surprisingly, further add to the inter-observer disagreement[12]. Training such AI models requires lots of human effort to make the labeled training data that should include all disease spectrum of severity available. Because of these technical and logistic issues, developing a semi-automated model (rather than fully-automated) is a reasonable alternative. Mahapatra *et al*[13,14] successfully developed their own semi-automated classification model to segment the affected bowel regions in CD patients using MRI data and achieved excellent results, required less training time, fewer labeled training samples and less expert effort when compared to their own fully-automated model.

Table 1 Artificial intelligence implications in the interpretation of radiography in inflammatory bowel disease patients

Ref.	Purpose	AI/DL model	Design	Result
Stidham <i>et al</i> [11], 2020	To identify structural bowel damage in IBD patients using AI-guided CT image analysis	semi-automated	Retrospective	Structural bowel damage measurements collected by semi-automated approaches are comparable to those of experienced radiologists
Mahapatra <i>et al</i> [13], 2016	To evaluate and compare semi-automated to fully automated models in identifying affected bowel segments in MRI of IBD patients	Semi-automated	Retrospective	Semi-automated model outperformed the fully automated model in the ability to segment the affected bowel regions in CD patients using MRI data with less required training time, training samples and expert effort

IBD: Inflammatory bowel disease; AI: Artificial intelligence; DL: Deep learning; CD: Crohn's Disease; CT: Computed tomography; MRI: Magnetic resonance imaging.

AI-guided interpretation of endoscopic images and capsule systems

The interpretation of endoscopic image analysis is of a great interest to the research community and is a main focus and a top priority for the AI ASGE Task Force[7], and is probably the fastest growing. Within the last 10 years, AI-guided endoscopic image analysis (images or videos) has been assessed in different scenarios (Table 2). For example, in 2015, Peng *et al*[15] developed an ANN to study the seasonal variation effect on the onset, relapse and severity of IBD patients. Assigning IBD (UC and CD) patient from 2003 to 2010 as a training cohort, the researchers utilized several meteorological data as an input layer {maximum temperature, minimum temperature, maximum air pressure, minimum air pressure, and humidity} and validated their model on a cohort of IBD patients from the year 2011. This ANN was able to predict the frequency of relapse with a great accuracy (Mean square error = 0.009, Mean absolute percentage error = 17.1%). However, this model had limited ability to predict the onset and severity of IBD.

Later in 2019, Maeda *et al*[16] developed a SVM model to predict the persistence of histologic inflammation in UC patients using endoscopic images. In this retrospective study, the researchers collected data from 187 patients with UC who had endoscopic observation followed by biopsy. Data and images from 87 patients were used to train the model and the remaining 100 patients were assigned for validation. This model achieved an impressive sensitivity, specificity, and accuracy of 74% [95% confidence interval (CI): 65%-81%], 97% (95%CI: 95%-99%), and 91% (95%CI: 83%-95%), respectively, with a great reproducibility.

The importance of the gastrointestinal tract evaluation (ex: *via* endoscopy) largely stems from its ability to predict the clinical outcome and response[17]. However, CD is usually evaluated *via* colonic and terminal ileum visualization and biopsy without a pan-enteric evaluation in spite of the high prevalence of proximal small bowel involvement in more than 50% of patients and its weight on the prognosis[18]. In an attempt to address this defect, a panenteric capsule system (Pillcam Crohns Capsule, Medtronic, Dublin, Ireland) has been recently developed, approved and integrated into the clinical practice[19], however; as with endoscopic means this system was also subject to the inter-observer variability of the human being during image analysis.

In response to these challenges, Gottlieb *et al*[20] conducted an interesting prospective multinational clinical trial using a DL algorithm in 2020 to score the severity of UC from full-length endoscopy videos. In this trial, researchers prospectively collected panenteric videos from a phase 2 clinical trial evaluating mirikizumab use in UC patients from 14 countries. In the first stage, a CNN was used to grade single frames, and in the second stage a recurrent neural network was used to aggregate the grading throughout the entire film. 795 full-length endoscopy videos were obtained from 249 patients, with 19.5 million image frames being assessed. Model's scores were compared to one endoscopic Mayo score (eMS) and one UC Endoscopic Index of Severity (UCEIS) scored by expert human subjects. The inter-rater agreement between either side predictions was compared using quadratic weighted kappa (QWK) metric and showed outstanding results, with a QWK of 0.844 for eMS (95%CI: 0.787-0.901) and 0.855 for UCEIS (95%CI: 0.80-0.91). Interestingly, this study also showed a good performance at the area of large inter-observer variability. For example, for eMS scores of 1 and 2 where the inter-observer variability is substantial, the model showed a specificity of 92% and 76.92% respectively; and a sensitivity of 64.71% and 60%, respectively.

Table 2 Artificial intelligence implications in the interpretation of endoscopic and capsule images of inflammatory bowel disease patients

Ref.	Purpose	AI/DL model	Design	Result
Peng <i>et al</i> [15], 2015	To predict the seasonal variation effect on the onset, relapse and severity of IBD patients	ANN	Retrospective	Great accuracy in predicting the frequency of relapse (Mean square error = 0.009, Mean absolute percentage error = 17.1%)
Maeda <i>et al</i> [16], 2019	To predict the persistence of histologic inflammation in ulcerative colitis patients using endoscopy images	SVM	Retrospective	Sensitivity, specificity, and accuracy of 74%, 97%, and 91%, respectively
Gottlieb <i>et al</i> [20], 2020	Determine the severity of UC from full-length endoscopy videos	CNN	Prospective	Inter-rater agreement factor (QWK) of 0.844 for eMS and 0.855 for UCEIS
Takenaka <i>et al</i> [21], 2020	To identify histological remission using colonoscopy images	Deep Neural Network	Prospective	Histologic remission identified with 92.9% accuracy
Stidham <i>et al</i> [22], 2019	To identify remission from disease group using colonoscopy images	CNN	Retrospective	Successfully identified the remission from the moderate-to-severe disease group with an AUROC of 0.966, a sensitivity of 83.0%, a specificity of 96.0%, PPV of 0.87, and a NPV of 0.94

AI: Artificial intelligence; DL: Deep learning; ANN: Artificial neural networks; SVM: Support vector machines; AUROC: Area under the receiver operating characteristic curves; NPV: Negative predictive value; PPV: Positive predictive value; CNN: Convolutional neural network.

One of Gottlieb *et al* [20]'s novelty was that their model was trained using videos rather than images and therefore allowed for a full model autonomy of prediction. However, image analysis itself has been previously implemented in other models. The two main models of endoscopic image analysis using AI algorithms were constructed by Takenaka *et al* [21] and Stidham *et al* [22] separately in the same year. In their model, Takenaka *et al* [21] trained their algorithm (the deep neural network for evaluation of UC, or DNUC) using retrospectively-obtained endoscopic images from UC patients who also underwent histological evaluation (biopsy) from 2014 to 2018. The DNUC algorithm was then prospectively validated using a real-time image analysis from a second cohort of UC who underwent endoscopic evaluation with biopsy from 2018 to 2019. The DNUC was able to correctly identify histologic remission with 92.9% accuracy, denoting the potential future ability of AI to identify endoscopic and histological remission without the need for mucosal biopsy.

Similarly, Stidham *et al* [22] constructed a multi-layer CNN model to categorize the images into a remission group (defined by Mayo subscore 0-1) and a moderate-to-severe disease group (defined by Mayo subscore 2-3). These images were also graded by two expert reviewers, and weighted κ agreement was used to measure model-reviewer agreement. The model was trained using retrospectively-obtained images from 3082 UC patients. The researchers used 90% of the cohort to train the model and 10% for validation. In the last step, the model underwent external validation using 30 full-motion colonoscopy videos to simulate real-life scenario. This CNN showed a great ability to distinguish between the remission and the moderate-to-severe disease groups with an area under the receiver operating characteristic curves (AUROC) of 0.966, a sensitivity of 83.0%, a specificity of 96.0%, a positive predictive value of 0.87, and a negative predictive value of 0.94. The agreement between the CNN-scored images and the human-scored images was also fairly good ($\kappa = 0.84$; 95% CI: 0.83-0.86) and very close to the agreement in between the two human experts ($\kappa = 0.86$; 95% CI: 0.85-0.87).

AI-GUIDED INTERPRETATION OF GENOMICS

The use of AI in the interpretation of gene expression has also been infrequently described (Table 3). Several biomarkers like micro-RNAs, single nucleotide polymorphisms, or microbiota have been indicated to have discriminating potential for the differential diagnosis of IBD [23].

For example, Khorasani *et al* [24] has recently utilized the 240 IBD-risk loci identified by the Genome-wide association studies (GWAS) [25] to develop their own model in 2020. In this model, the researchers used a recently developed feature selection algorithm combined with SVM classifier to differentiate UC patients from healthy subjects based on the values of expression for 32 genes obtained from colon samples.

Table 3 Artificial intelligence implications in the interpretation genomic of inflammatory bowel disease patients

Ref.	Purpose	AI/DL model	Design	Result
Khorasani <i>et al</i> [24], 2020	To differentiate UC patients from healthy subjects using colon samples	SVM-DRPT	Retrospective	Predicted all active cases of UC with an average precision of 0.62 in the inactive cases
Wei <i>et al</i> [27], 2013	To predict the risk of IBD using genomic data of risk loci	Advanced ML techniques	Retrospective	Successfully predicted IBD with an unprecedented predictive power with AUCs of 0.86 for CD and 0.83 for UC

IBD: Inflammatory bowel disease; AI: Artificial intelligence; DL: Deep learning; CD: Crohn's Disease; UC: Ulcerative colitis; ML: Machine learning; SVM-DRPT: Support vector machines-developed feature selection algorithm.

This model was able to successfully predict all active cases of UC, with an average precision of 0.62 in the inactive cases. Despite the limitation of the training datasets (only two), this model outperformed BioDiscML[26] on the basis of average precision. Wei *et al*[27] had also previously utilized this large multinational GWAS data in synthesizing and validating their own IBD-risk predicting model by identifying the disease loci, and achieved an unprecedented predictive power with areas under the curve (AUCs) of 0.86 for CD and 0.83 for UC. Despite these interesting results, it is worth emphasizing that the use of genomic-based models is still in a very early stage of research and is not yet well-adapted in clinical practice.

AI AND IBD: TREATMENT AND FOLLOW UP

The most useful clinical application of AI might be in its potential ability to assess treatment effectivity and response to medications, and numerous studies have been published in this field (Table 4). Waljee *et al*[28-32] published few studies where they assessed treatment response using AI. In one study[28], they developed their algorithm using phase-3 clinical trial data on Vedolizumab for CD from GEMINI I and II assessing corticosteroid-free remission at week 6 and week 52. Patients predicted to be in corticosteroid-free remission by the algorithm achieved the endpoint 35.8% of the time at week 52, but only 6.7% of the time at week 6. This algorithm was able to predict with reasonable accuracy as to which patients were unlikely to achieve remission at week 6. In a similar design, Waljee *et al*[29] developed a machine algorithm to predict durable response to Ustekinumab in patients with CD[29]. They analyzed data from three phase-3 randomized clinical trials (UNITI-1, UNITI-2, and IM-UNITI) and built 2 models, the first using only baseline data and the second using data till week 8. The week-8 model had an AUROC of 0.78 (95%CI: 0.69-0.87). In the testing data set, about 49% patients classified as likely to achieve clinical success did actually achieve it after week 42, while only about 11% achieved remission in those classified as likely to have treatment failure.

Another study by Waljee *et al*[30] aimed to assess an algorithm to predict thiopurine non-responders, nonadherence and shunters[30]. In this study, the researchers used laboratory and age data for algorithm training and compared it to thiopurine metabolite measurement in predicting the outcomes. The algorithm was able to differentiate clinical responders from non-responders with AUROC curve of 0.856, while the thiopurine metabolite had AUROC curve of 0.594 ($P < 0.001$), and hence this ML model demonstrated a clean superiority in outcome prediction compared to the laboratory measurement. This algorithm was further externally validated on the SONIC clinical trial data set[31]. This method is clinically quite relevant, as the data used by the algorithm are readily available and very cost effective.

A similar study by Waljee *et al*[32] developed an algorithm using laboratory values and age to identify IBD patients in objective remission on thiopurines and to assess if the algorithm was able to predict fewer clinical events as compared to measurement of thiopurine metabolites[32]. The clinical events were defined as new steroid prescriptions *per year*, hospitalizations *per year* and surgeries *per year*. For objective remission, the algorithm was superior to thiopurine metabolite measurement and statistically significant, with AUROC of 0.79 (95%CI: 0.78-0.81) *vs* 0.49 (95%CI: 0.44-0.54), respectively, and P value of $< 2.2 \times 10^{-16}$. In patients with sustained algorithm-predicted remission, statistically significant reduction in steroid prescriptions/year and hospitalizations *per year* were seen, proving the superiority of the machine-learning algorithm to thiopurine metabolite measurement.

Table 4 Artificial intelligence implications in the treatment and prognosis of inflammatory bowel disease patients

Ref.	Purpose	AI/DL model	Design	Result
Waljee <i>et al</i> [28], 2018	To predict corticosteroid-free biologic remission	Random Forest modeling	Retrospective	At week 52, patients predicted to fail succeeded 6.7% of the time
Waljee <i>et al</i> [29], 2019	To predict long-term response to ustekinumab	Random Forest modeling	Retrospective	Per week-8 model, only 11% predicted to fail achieved remission
Waljee <i>et al</i> [30], 2010	To predict response to thiopurines	Random Forest modeling	Retrospective	The model was superior to metabolite measurement in predicting non-responders.
Waljee <i>et al</i> [31], 2018	To externally validate previously developed thiopurine algorithm	Random Forest modeling	Retrospective	The algorithm accurately predicted objective remission with AUROC 0.76
Waljee <i>et al</i> [32], 2017	To identify patients in objective remission on thiopurines and analyze if these patients had fewer clinical events <i>per year</i>	Random Forest modeling	Retrospective	AUROC for algorithm-predicted remission was 0.79 <i>vs</i> 0.49 for thiopurine metabolite proving model superiority

AUROC: Area under the receiver operating characteristic curves; AI: Artificial intelligence; DL: Deep learning.

AI AND IBD: PROGNOSIS AS DETERMINED BY THE MACHINE

Similar to studies on treatment response, AI has also been shown to have a significant potential in the prognostication of IBD patients (Table 3). Waljee *et al* [33] developed two machine learning models using clinical parameters to predict hospitalization and outpatient corticosteroid use for IBD within 6 mo [33]. The AUROC for the random forest longitudinal model using previous hospitalization or steroid use was 0.87 (95% CI: 0.87–0.88). The accuracy of the model was significant, which would allow for a personalized management of high-risk patients. Genome wide association studies and microbiome data have also been used in some studies in addition to the referred earlier. For example, a study by Cushing *et al* [34] used RNA extraction and human transcriptome microarray from mucosal biopsies of uninfamed tissue from operative specimens after ileocolic resection in CD patients. Their study showed that anti-tumor necrosis factor -naïve and -exposed patients have unique expression profiles at the time of surgery, which may be utilized to assess the risk of non-recurrence.

Morilla *et al* [35] conducted a study on patients with acute severe UC to predict the response to steroids, infliximab and cyclosporine. They used microarray analysis of microRNA expression profiles from colon biopsy specimens. Their deep neural network-based classifier was able to identify 9 microRNAs plus 5 clinical factors associated with response to treatment. Their panel discriminated between steroid responders and non-responders with 93% accuracy (AUC = 0.91). Based on microRNA levels, they developed three algorithms that distinguished responders to infliximab from non-responders with 84% accuracy (AUC = 0.82), and responders to cyclosporine from non-responders with 80% accuracy (AUC = 0.79).

CONCLUSION

AI has been widely applied in multiple medical sciences [3–6]. Among its numerous applications in the field of gastroenterology, AI implications in IBD seems to be the fastest growing and the most promising (Tables 1–4). This has been largely driven by the tremendous availability of data which necessitates finding a path to efficiently utilize it in a safe and cost-effective manner. The ultimate goal of AI is to provide a human-independent interpretation of the data to allow for a standardized diagnostic process and minimize the inter- and intra-rater variability. The patient-tailored management is an extra-privilege that AI can also provide using its complex neural algorithm's ability to understand the non-linear interactions between the factors contributing to IBD, build on it and predict the result. Given the tremendous availability of the data, AI is expected to save time, effort and money. However, training a model and validating it would –at least initially– require all three of these, which makes the AI industry very challenging. Most of the current models were validated retrospectively which limits the external validation. More prospectively-validated models are needed for the medical community to familiarize with AI if it's to be adopted by physicians and integrated into their clinical practice.

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