**Artificial Intelligence and Endo-Histo-OMICs: New Dimensions of Precision Endoscopy and Histology in Inflammatory Bowel Disease**

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**Abbreviations:** AI,artificial intelligence; CD, Crohn’s disease; CDS, cumulative disease score; CNN, convolutional neural network; CT, computed tomography; DL, deep learning; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; IUS, intestinal ultrasound; GHAS, Global Histology Activity Score; MES, Mayo Endoscopic Score; ML, machine learning; MR, magnetic resonance; NHI, Nancy's Histopathology Index; pCLE, probe-based confocal laser endomicroscopy; PICaSSO, Paddington International Virtual Chromoendoscopy Score; PHRI, PICaSSO Histologic Remission Index; RD, red density; RHI, Robarts Histopathology Index; TNF, tumour necrosis factor; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; VCE, virtual electronic chromoendoscopy; WLE, white-light endoscopy.

**Summary**

Integrating Artificial Intelligence (AI) into inflammatory bowel disease (IBD) revolutionises clinical practice and research. AI harnesses advanced algorithms to deliver accurate assessments of IBD endoscopy and histology, offering precise evaluations of disease activity, standardized scoring, and outcomes prediction. Furthermore, AI offers the potential for a holistic "Endo-Histo-OMICs" approach by interlacing and harmonizing endoscopy, histology, and OMICs data towards precision medicine. It is without doubt that the emerging applications of AI may pave the way for personalised medicine in IBD, offering patient stratification for the most beneficial therapy with minimal risk. While AI holds promise, challenges remain, including data quality, standardisation, reproducibility, clinical implementation, ethical concerns, legal liability, and regulatory issues. The development of standardized guidelines and interdisciplinary collaboration, including policymakers and regulatory agencies, is crucial for addressing these challenges and advancing AI in IBD clinical practice and trials.

**Keywords:** advanced endoscopy**;** artificial intelligence; Endo-Histo-OMICs; endoscopy; histology; Inflammatory Bowel Disease; OMICs; precision medicine

**Introduction**

Artificial intelligence (AI) harnesses computational systems to tackle challenges that typically require human knowledge.1 The application of AI in medicine, facilitated by innovative algorithms, i.e. Machine Learning (ML), deep learning (DL) models and neural networks, is reshaping scientific research and medical care. Specifically, the application of AI models in medical imaging offers several tangible benefits, including accurate data evaluation, decreased inter- and intra-observer variability, enhanced detection of subtle details imperceptible to the human eye, improved granularity measures, pattern recognition, and outcome prediction, ultimately aiding patient management and resource optimisation related to time and cost.

Several medical disciplines relying on imaging data have witnessed significant advancements by integrating AI into image analysis, leading to the Food and Drug Administration's (FDA) recent approval of numerous AI-enabled medical devices.2,3 Indeed, AI has proven its capability to detect diabetic retinopathy, glaucoma, and age-related macular degeneration when applied to fundus photographs, optical coherence tomography, and visual fields.4 Likewise, AI exhibits promising potential in oncology and radiology for automatically identifying and categorising neoplastic lesions observed in thoracic and abdominal imaging, including X-ray, computed tomography (CT) and the more challenging magnetic resonance (MR) imaging.5,6 Furthermore, AI applications can aid in image-based diagnoses of conditions such as stroke and heart diseases.7

In this dynamic landscape, AI has revealed significant potential to revolutionise inflammatory bowel disease (IBD) imaging practices, spanning advanced endoscopy and histology in clinical trials and real-world healthcare settings. Although advanced imaging techniques in IBD, including virtual electronic chromoendoscopy (VCE) and histology-like imaging methods like probe-based confocal laser endomicroscopy (pCLE) and ultra-high magnification endocytoscopy, have rapidly evolved, challenges in interpretation persist.8 Moreover, the reliance on human central readouts for standardising endoscopic and histological scoring needs to be more objective, extremely time-consuming, and costly. AI might play a pivotal role in overcoming these challenges by providing accurate and rapid assessment of disease activity. Additionally, it can interpret advanced endoscopic imaging and digital histological slides to predict outcomes and enhance treatment decisions.

Remarkably, AI holds potential in transforming IBD patient assessment and management through seamless integration of endoscopy and histology information with large multi-OMICs “big data”,9 translating into useful multimodal predictive clinical tools. Therefore, AI and precision medicine represent a potential perfect pairing in IBD to address challenges in harnessing data and tailor unique patient care approaches.

This review aims to delve into the impact of AI applications on IBD endoscopy and histology and underscore the role of ML models in harmonising endoscopy, histology and OMIC techniques. This “Endo-Histo-OMICs” approach heralds a new era of precision medicine in IBD.

**Search Strategy And Selection Criteria**

References for this Review were identified in December 2023 through searches of PubMed with the search terms “Inflammatory Bowel Disease”, “Ulcerative Colitis”, “Crohn’s Disease”, “Endoscopy”, ”Advanced imaging”, “Endocytoscope”, “Confocal laser endomicroscopy”, “Histology”, “OMICs”, “RNA Transcriptomics”, “Microbiome”, “Precision Medicine”, “Machine Learning”, “Deep Learning” and “Artificial Intelligence” for all articles published since database inception. Articles were also identified through the reference list of pivotal review articles for additional papers judged to be relevant to this review. The final reference list was generated based on originality and relevance to the broad scope of this Review.

**1. AI in IBD Endoscopy**

Endoscopic imaging is considered the gold standard for diagnosing and assessing IBD. Mucosal healing, characterised by the regression or disappearance of endoscopic lesions, is a primary treatment goal in IBD.10 Advanced endoscopic technologies already available in clinical practice, including VCE, pCLE and ultra-high magnification endocytoscopy, enable a detailed and refined characterisation of the mucosal and vascular architecture at surface and ultrastructural level. Thus, endoscopic imaging is getting closer to histology and propelling the boundaries of precision endoscopy. These tools offer a remarkable ability to predict long-term outcomes and treatment responses.11 Nonetheless, the persistence of subjectivity in disease assessment and high inter- and intra-observer variability in scoring systems, even among experts, continue to pose significant challenges.

By employing advanced algorithms tailored for endoscopy, AI can accurately assess disease activity and enable standardized scoring of images. Therefore, AI has the potential to enhance the precision and granularity of IBD evaluation in both trials and clinical practice, providing a reliable foundation for disease management (Figure 1). Table 1 provides an overview of the main studies investigating AI models in IBD endoscopy.

* 1. *AI-Guided IBD Endoscopy Assessment*

*a) For White Light Endoscopy*

Over the past few years, several scoring systems have been developed and validated for endoscopic assessment of IBD. These are crucial for guiding targeted treatment and predicting long-term disease outcomes.12 However, these are subjective, operator-dependent and limited by inter- and intra-observer variability even in experts' hands.

Recently, several AI algorithms have been developed to accurately grade disease activity across various endoscopic scoring systems in ulcerative colitis (UC) to overcome these limitations, showing excellent diagnostic performance and strong concordance with experts.13-23 Overall, a recent meta-analysis including 12 studies revealed that convolutional neural network (CNN)-based DL algorithms for assessing UC severity had a pooled accuracy of 91.5%, with a high sensitivity of 82.8% and specificity of 92.4%.24 Sensitivity and positive predictive values were significantly higher for the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) scoring system compared with Mayo Endoscopic Score (MES) 94% vs 82% and 94% vs 84%, respectively, with no significant difference in specificity and accuracy. Similarly, another recent systematic review and diagnostic test accuracy meta-analysis confirmed high potential of CNN-based DL algorithms in detecting mucosal healing in UC.25 However, moderate-high levels of heterogeneity were found, limiting the quality of evidence and clinical application.

Encouraging results stem from a recent study by Stidham *et al.* evaluating an automated and quantitative measure of global endoscopic disease severity, the cumulative disease score (CDS).26 The CDS was significantly associated with MES, and all partial Mayo score clinical components exhibited higher sensitivity than MES in distinguishing between ustekinumab and placebo treatment response (Hedges’ g=0.743 vs 0.460). Considering the diffuse yet at times patchy nature of UC disease, a system capable of assessing inflammatory activity automatically throughout the entire colon holds promise for a more comprehensive evaluation, long-term outcomes prediction and treatment responses in both clinical trials and clinical practice. Further evidence of its application is required.

Moreover, recently developed Red Density (RD), a digital endoscopic tool, can also calculate the grade of inflammation in UC using an automated RD score based on assessing redness on a pixel level.27 In the validation study, the algorithm exhibited a significant but moderate correlation with MES and UCEIS (r 0.61 and 0.56, respectively) and histologic scores (*r* 0.65) in UC.

Few studies have evaluated the application of AI on Crohn’s disease (CD) imaging, given its transmural involvement; however, these are mostly focused on small bowel assessment by capsule endoscopy.28 Recently, a DL model was employed to assist pan-enteric capsule endoscopy by presenting a subset of the acquired data to human readers.29 Reviewing the DL-selected pictures, 2 observers achieved a sensitivity of 96% and 92% and a specificity of 93% and 90%, respectively. Moreover, the AI-assisted image analysis significantly reduced the total number of images for review (from 2.965.900 to 86.129, 97.1% reduction) and the review time (pooled median review time of 3.2 min per patient) thus potentially enhancing efficiency, accuracy and practical application.

*b) For Advanced Imaging Techniques*

Emerging advanced imaging technologies have been used for *in vivo* assessment of ultrastructural features of the bowel mucosa resembling real-time histology, i.e. VCE, endocytoscope, and pCLE.8 Although most AI models have been designed for white-light endoscopy (WLE), Iacucci *et al.* developed the first CNN using both WLE and VCE videos to grade endoscopic activity in UC by UCEIS and the new Paddington International Virtual Chromoendoscopy Score (PICaSSO).30,31 The system performed better in detecting endoscopic remission for VCE by PICaSSO than for WLE by UCEIS - sensitivity 79% vs 72%; specificity 95% vs 87% and AUROC 0.94 vs 0.85. Conversely, the prediction of histologic remission was similar between WLE and VCE.

The endocytoscope (Olympus, Japan) enables detailed real-time histology-like evaluation of the mucosal surface, offering up to 520-fold magnification in assessing crypt architecture, cellular infiltration, and micro-vessel impairment. The integration of AI with endocytoscope, known as EndoBRAIN-UC (Cybernet system, Tokyo, Japan), was introduced by Maeda *et al.* and showed good accuracy in predicting endoscopic and histological activity according to morphological changes of capillaries in the colonic mucosa.32

Similarly, pCLE provides visualisation of mucosal layer at cellular and sub-cellular levels, using intravenous fluorescent agents, resulting in highly magnified images reaching up to 1000-fold magnification. This technique is pioneering the evaluation of the intestinal barrier's structural and functional integrity.33 A promising computer-based model analysis on pCLE, based mainly on crypts, vessel architecture, and fluorescein leakage, accurately diagnosed IBD and assessed mucosal healing.34,35

Overall, AI has made remarkable progress in aiding disease assessment, demonstrating a robust correlation with histopathological findings, which is essential in clinical practice and clinical trials. AI is a transformative force in interpreting endoscopy imaging, offering high reproducibility, speed, and standardization. It will contribute to simplifying advanced imaging by reducing training and implementing these technologies in clinical practice.

* 1. *AI-guided IBD Endoscopy Prediction of Response to Therapy and Outcomes*

The integration of AI with endoscopy extends beyond diagnosis to encompass outcomes prediction. AI-driven endoscopy has demonstrated the ability to predict colitis disease trajectories and clinical outcomes, enhancing patient management. However, validation on a large cohort of patients is required to confirm the reproducibility of AI-powered systems.

For instance, the AI-PICaSSO model showed a strong association between AI-assessed disease activity and risk of adverse outcomes (HR 4.05), consistent with human endoscopist findings (HR 4.59).31 Similarly, the DNUC algorithm developed by Takenaka *et al.* predicted clinical outcomes comparable to physician-assessed endoscopy scores at 12 months (HR for hospitalization, colectomy, steroid use, and relapse of 48.4, 46.4, 10.2, and 8.8, respectively).36 Also, the EndoBRAIN-UC has demonstrated the ability to predict clinical relapse rate at 12 months (28.4% in the AI-active group vs 4.9% in the AI-healing group, p<0.001).37

In addition, AI has demonstrated promising potential to predict therapy responses for IBD by combining computer-aided *in-vivo* and *ex-vivo* pCLEimage analysis with genomic data, which has shown in an exploratory study the ability to predict the response to biological therapy.9 Such ‘fusion’ of multidimensional data (Endo-omics) now needs widespread testing to drive precision medicine in IBD.

Integrating AI with endoscopy in IBD extends beyond diagnostic applications by forecasting disease trajectories and clinical outcomes. This, in turn, can enable the potential for personalized treatment strategies and improved patient care.

*1.3 AI-guided IBD Endoscopy Dysplasia Detection*

An important and crucial aspect of IBD endoscopy is its role in dysplasia surveillance.37 Although the efficacy of dye-assisted endoscopy and targeted biopsy protocols as potential alternatives to conventional random biopsy protocols is increasingly accepted,38 early-stage IBD-related dysplasia detection is still challengingand is expected to improve with electronic chromoendoscopy and AI. Several computer-aided AI detection systems have already been clinically implemented to detect colorectal lesions in non-IBD patients.39 This stands out as a prominent advancement in AI-driven colonoscopy. However, its applicability in patients with IBD has yet to be explored and requires further investigation.40 Some encouraging results have been recently presented by Vinsard *et al*.41 Their novel computer-aided model for detecting colorectal lesions in IBD showed high sensitivity and specificity, mainly when applied to HD-WLE, with 95% sensitivity, 99% specificity, 95% accuracy and 0.85 AUC. Such developments promise to enhance the performance of surveillance colonoscopy in IBD.

**2. AI in IBD Cross-sectional Imaging**

Despite endoscopy being the gold standard for IBD diagnosis and assessment, cross-sectional imaging is increasingly used as a complementary technique for disease monitoring and detecting complications.42 Recommended techniques include CT, MR enterography, and intestinal ultrasound (IUS), with the latter being notable for its widespread availability, safety, and cost-effectiveness.43 However, the accuracy of image interpretation may be influenced by operator expertise, and significant inter- and intra-observer variability has been reported for this technique.44 AI offers an opportunity to address these challenges.45 While AI models based on CT and MR enterography (radiomics) have shown promise, AI in IUS is still evolving. Carter *et al*. recently developed and validated a CNN able to distinguish bowel wall thickening suggestive of bowel inflammation from normal bowel.46 This model demonstrated an overall excellent performance, with sensitivity, specificity, accuracy, and AUC of 86.4%, 94%, 90.1%, and 0.97, respectively. Further studies are warranted, but AI models for automatically detecting inflammatory-related changes could greatly aid in standardising image interpretation and scoring in clinical practice and trials, ultimately improving patient management.47-49

**3. AI in IBD histology**

Histological remission is an emerging treatment target in IBD clinical practice and trials.10,50 Clinical and endoscopic remission may still harbour an underlying active histological disease, making microscopic inflammation a pivotal indicator of disease activity and prognosis.51 However, advanced endoscopic imaging is getting closer to histology in predicting outcomes. Ensuring the precision and reliability of histological analyses is thus of utmost importance. Robarts Histopathology Index (RHI), Nancy's Histopathology Index (NHI), and Geboes's score are the recommended tools, especially for UC. 52,53

Nevertheless, conventional histological evaluations face several limitations,54 including limited real-world application of histological scoring systems, often restricted to experts in the field and time-consuming. Furthermore, subjectivity in interpretation can compromise the accuracy and reproducibility of histological analyses.55 The rapid introduction of digital scanning of histopathology slides has accelerated AI-enabled histologic scores, heralding a paradigm shift in IBD care (Figure 2). Table 2 provides an overview of the main studies investigating AI models in IBD histology.

*3.1 AI-guided IBD Histology Assessment*

A pioneering attempt to standardize biopsy interpretation emerged when Matalka and colleagues introduced an advanced image processing technique to automatically assess crypt architecture distortion and mucosal damage for IBD diagnosis.56 This system, evaluating 118 biopsies, demonstrated an overall precision rate exceeding 98% compared to the consensus of three expert pathologists.

Further, a significant milestone was achieved by developing the first DL algorithm designed to identify eosinophils as markers of active UC.57 When applied to colonic biopsies from 88 patients with active UC, this algorithm perfectly agreed with manual eosinophil counts performed by pathologists (ICC=0.81-0.92). However, eosinophil density did not correlate well with histological activity, and the current consensus among international experts places greater pathogenic significance on neutrophils.52,58

Noteworthy, the PICaSSO consortium introduced a considerably simplified histological score called the PICaSSO Histologic Remission Index (PHRI), based solely on the presence of neutrophils, to assess remission in UC.59 This score displayed a robust correlation with endoscopic scores and achieved perfect inter-rater agreement (ICC 0.84). Employing a novel PHRI-based DL strategy built upon a CNN architecture, the group analysed 614 digitized biopsies from a multicentre cohort of 302 UC patients. This approach showed promising results in predicting the histological remission with accuracy rates of 80% and 79% in the validation and testing sets, respectively. Subsequently, the group trained a novel CNN-based framework, using an innovative multiple instances learning framework with location constraints,60 capable of detecting UC activity based on neutrophils through assessment of PHRI, RHI, and NHI.61 This new system exhibited high sensitivity and specificity in distinguishing and predicting histologic activity and remission.

More recently, Peyrin-Biroulet and colleagues introduced an AI-driven scoring system for UC histology based on NHI, demonstrating a high correlation with histopathologists (ICC=87.20).62 However, specific diagnostic metrics were not reported.

Of note, automated segmentation of pathology images has gained increasing interest.63 A pioneering CNN model, performing tissue and cell segmentation and quantifying histologic features related to UC activity, has been recently developed and validated by Najdawi and colleagues.64 The tissue and cell model-generated human-interpretable features strongly correlated with disease severity and pathology-assigned NHI score. Also, a Random Forest classifier based on these features could predict NHI score, with performance like pathologists (k=0.91; ⍴=0.89), and histological remission (accuracy 0.97).

There is currently limited data available for the application of AI in CD histology. However, a noteworthy development is a DL model developed by Kiyokawa *et al*.65 This model, analysing 550 slides of surgical specimens, achieved a high level of accuracy in predicting postoperative CD recurrence (AUROC 0.995) and found adipocyte shrinkage and mast cell infiltration as histological features related to recurrence.

Recently, Rymarczyk *et al*. introduced novel DL models for automating histological assessment of CD and UC histological images from phase 2 and phase 3 clinical trials.66 The AI-modelled Global Histology Activity Score (GHAS) in CD and Geboes subgrades matched central reading with moderate to substantial agreement, achieving accuracies between 80% to 89% for GHAS in the colon, 65% to 82% for GHAS in the ileum, and 65% to 85% for Geboes scale.

AI in IBD histology has witnessed significant progress, holding promise in refining diagnostic accuracy, thereby assisting clinicians in decision-making. However, the field requires further exploration and refinement of diagnostic metrics before these can be adopted in clinical practice and trials.

*3.2 AI-guided IBD Histology-Based Prediction of Outcomes*

AI-aided histology in UC has also demonstrated predictive ability regarding clinical outcomes. The pioneering CNN model developed by Iacucci et al. exhibited high sensitivity and specificity in stratifying the risk of flare at 12 months between histological activity/remission groups according to PHRI, similar to human pathologists (HR 4.64 vs. 3.56, respectively).61

Despite facing challenges, such as the standardisation of tissue collection and biopsy procedures and the necessity for validation across extensive data, AI can analyse extensive histological datasets swiftly and with unparalleled precision and accuracy, moving towards personalized pathology. Hence, its utility in IBD extends beyond clinical practice to streamline large-scale clinical trials, expediting the development of innovative therapies.67

**4. Impact of AI Endoscopy and Histology on Clinical Practice**

Despite the limited utilization of AI in current clinical practice, its immense potential will drive its progressive integration into medical routine.

The automation and accuracy offered by AI in endoscopic assessment and scoring hold significant promise in defining endoscopic and histologic healing as a treatment target, mitigating inter- and intra-observer variability and enhancing treatment decision-making and patient outcomes.68 As mentioned, numerous AI models applied to white-light and advanced endoscopy have demonstrated exceptional performance in identifying mucosal healing. The application of AI for complex imaging would enable fast and standard interpretation of subtle ultrastructural changes including gut barrier that may elude the human eye, reducing human errors, training and the need for biopsies in daily practice.67 AI-aided endoscopy has also shown promise in predicting treatment outcomes, leading to precise patient disease stratification and assisting physicians in making real-time, accurate treatment decisions.

Similarly, AI's role in histology is invaluable, to accurately differentiate active from quiescent microscopic disease and predict histological remission.

Moreover, AI's predictive capabilities are pivotal in anticipating disease flares, identifying potential complications, and forecasting therapy responses. This can assist physicians in decision-making, enabling timely interventions and personalised treatment decisions, thereby enhancing the management of patients with IBD.

**5. Impact of AI Endoscopy and Histology on Clinical Trials**

Clinical trials stand as the cornerstone in shaping the future of our understanding and management of IBD. An escalating enthusiasm surrounds exploring novel therapies as the medical community seeks breakthroughs to surmount the existing therapeutic ceiling.69 Regulatory agencies worldwide are advocating for mucosal healing as the primary endpoint in trials and, additionally, recent international consensus has underscored the significance of histological remission as a crucial goal in UC and CD.52,70,71

Nevertheless, the persistent challenges of inter- and intra-observer variability and the different expertise among endoscopists and pathologists contribute to the suboptimal assessment of disease in clinical trials.72,73 This can lead to the inappropriate enrolment of patients, incorrect treatment arm assignment, and the inaccurate characterisation of therapy response. Furthermore, pursuing greater accuracy through central reading can lead to significant increased costs, prolonged turnaround times, and frustrating delays.72,74 In this scenario, AI, with its capability to revolutionise endoscopy and image interpretation, represents the fuel for advancing IBD clinical research. The integration of AI with electronic health records systems and specialised registries can facilitate the efficient and prompt identification of large cohorts of potentially eligible patients, thereby assisting in their enrolment in clinical trials.73 Additionally, AI-enabled accurate disease assessment and scoring can potentially lead to a reduction in the necessary sample size for clinical trials.26 Furthermore, AI can offer a more precise identification of treatment response and non-response,eliminating the delays associated with central reading, speeding up clinical trials and drug discovery.75,76 It is worth noting that the cost-saving benefits demonstrated in AI-guided colonoscopy for polyp diagnosis in clinical trials, up to 18.9% and US$149.2 million, offer a promising perspective for cost efficiency in IBD trials.77

AI’s potential extends further, integrating diverse data types from IBD datasets, including clinical, endoscopic, histologic, and OMICs, enabling a multi-parametric analysis that can further enhance the quality of clinical trial outcomes towards precision medicine.78

Nevertheless, several challenges persist in its application in clinical trials, including human-related diverse datasets selection, categorisation biases, imaging standardization, preserving patient privacy, cybersecurity concerns to prevent malicious attacks which will affect trial validity.Formulation of rigorous guidelines and attention to bias will be the key next stage.

**6. Precision “Endo-Histo-OMICs” Enabled by AI in IBD**

*6.1 A New Era of “Endo-Histo-OMICs”*

Conventional endoscopic and histological assessment of disease activity alone have limitations in predicting therapeutic outcomes, highlighting the need to explore innovative approaches.79 The “Endo-Histo-OMICs” approach, which interlaces endoscopy, histopathology, and OMIC techniques, such as genomics, transcriptomics, proteomics, and metagenomics, emerges as a promising tool to enhance the understanding of pathogenesis and management of IBD. This approach enables the detection of specific genes and molecular signatures of IBD, providing a comprehensive framework for unravelling its underlying mechanisms and identifying potential targets for patient-tailored treatment options.

Pilot studies have explored molecular imaging and endoscopy to predict IBD's therapeutic response. These techniques use [fluorescent probes](https://www.sciencedirect.com/topics/medicine-and-dentistry/fluorescent-dye) that specifically bind to molecular targets, enabling their identification through advanced endoscopic techniques, such as pCLE. In a study by Atreya *et al*., 25 CD patients were prospectively assessed using molecular imaging with fluorescent antibodies targeting tumour necrosis factor (TNF).80 A higher number of membrane TNF-expressing cells was associated with a greater likelihood of clinical response to adalimumab therapy, with sensitivity, specificity, and accuracy for predicting therapeutic responses of 92%, 85% and 88%, respectively. Similarly, Rath *et al.* employed molecular imaging to detect α4β7 integrin expression in a cohort of 5 CD patients before [vedolizumab](https://www.sciencedirect.com/topics/medicine-and-dentistry/vedolizumab) therapy.81 Their findings revealed that responders to treatment had peri cryptal α4β7+ cells, whereas non-responders did not have any α4β7+ cells.

Furthermore, Iacucci *et al.* pioneered the “Endo-Omics” approach, combining computer-aided image analysis of *in-vivo* and *ex-vivo* pCLE with RNA transcriptomics.9 In their exploratory study, 29 IBD patients were enrolled to predict response to infliximab and vedolizumab. *In vivo*, endomicroscopy findings defined as vessel tortuosity, crypt morphology, and fluorescein leakage predicted response to therapy in UC and CD patients, with an accuracy of 85% and 80%, respectively. *Ex -vivo*, increased binding of fluorescent-labelled biologics at baseline was associated with a higher likelihood of response, particularly in UC (AUROC 83%; accuracy 77%; PPV 89%; NPV 50%).Moreover, a panel of differentially expressed genes including ACTN1, CXCL6, LAMA4, EMILIN1, CRIP2, CXCL13 and MAPKAPK2 showed promise in predicting anti-TNF response (AUROC>0.7).

“Endo-Histo-OMICs” holds promise as a ground-breaking approach in IBD management, providing a proactive, individualized, and highly effective strategy by creating a comprehensive patient fingerprint and monitoring clinical, endoscopic, histological, and molecular changes over time (Figure 3).

*6.2 AI-aided “Endo-Histo-OMICs” Approach: Why Is It of Emerging Importance in Precision Medicine?*

IBD exhibits a broad spectrum of phenotypes, often challenging categorising patients into a single entity. They differ significantly in clinical presentation, endoscopic findings, histologic features, and molecular profiles. The advent of cutting-edge OMICs technologies has ushered in unprecedented “big data” for researchers and physicians studying and treating IBD.78,82 ML models, able to manage and decipher vast datasets, harbour the potential to untangle the intricate complexity of these diseases and revolutionise both research and clinical practice in IBD.

Pioneering studies have shown that an integrative approach can identify patient subgroups (phenomapping) for tailored disease management. This highlights the need to integrate all these multi-OMIC multifaceted data for comprehensive patient profiling.83,84

One of the primary advantages of the AI-aided fusion multimodal approach is the ability to identify and understand specific and interconnected biological alterations, enabling early and improved disease diagnosis and outcome.85 Furthermore, an integrated approach can identify biomarkers, a long unmet need that can play a critical role in early diagnosis, predicting treatment response, and monitoring disease activity, progression, and recurrence.86

The ability to foresee a disease's natural history and patient responses to therapy through AI algorithms would be invaluable.87 Indeed, in the “Endo-Omics” study,9 the integration, harmonisation and network organisation of multi-omics datasets, driven by the next generation “*in vivo”* advanced imaging-enabled AI, is poised to enhance precise decision-making by predicting and stratifying disease and personalising medical treatment.

As the IBD therapeutic armamentarium expands, a holistic approach can help move beyond the 'one-size-fits-all' paradigm, facilitating tailored therapeutic strategies.88 It can optimise drug selection, dosages, and treatment durations while minimising adverse effects. Moreover, AI models have the potential to enable real-time molecular monitoring of treatment efficacy and side effects, aiding clinicians in determining the most cost-effective treatment plan for each patient, thereby reducing healthcare costs, and improving budget management. Thus, the “Endo-Histo-OMICs” approach can enhance therapeutic research by prioritising drug targets and expediting drug development (Figure 4). Additionally, it can enhance translational research, improving its accuracy, reliability, and quality to translate these advances into clinical practice.

**7. Challenges of AI**

The application of AI and ML models in precision medicine holds promise but faces numerous challenges (Figure 5). These can be broadly summarised as data, reproducibility, explainability, and overconfidence challenges.

*7.1 Data Challenge*

One key challenge concerns the data quality used to build AI models. To create a robust and reliable AI system, high-quality data and an adequate sample size are essential to avoid misrepresentations and overfitting.89 Standardised data collection, well-defined datasets, and power calculations during study design are imperative to address this challenge. Moreover, AI models should be robust to different sources of variability. Therefore, it remains crucial to assemble datasets with diversity across acquisition tools and protocols and demographic and geographic statistics, among others.

*7.2 Reproducibility Challenge*

Reproducibility and generalizability are common issues in AI models, necessitating external validation using independent and diverse datasets to assess their performance and robustness before clinical application. However, a chasm between AI advancements and clinical implementation persists.90 Bridging this gap requires AI model transparency, suitability, and adaptability. A standardised methodology of AI-model development and interdisciplinary efforts from experts will be crucial to enhance the probability of AI translation into precision medicine approaches.91 Additionally, collecting large and expertly annotated datasets is impractical or time-consuming in the medical domain due to the subjectivity associated with the annotation protocol. This challenge leads to investigating unsupervised or weakly supervised learning frameworks such as multiple instance learning (MIL) commonly implemented for WSI automated analysis.92

Enhancing the reproducibility and transparency of AI models relies also on making training datasets publicly available. These datasets are foundational in building reliable models, and their open availability can facilitate researchers and organisations interested in AI and ML to develop suitable models and pinpoint potential biases. Consequently, it is essential to make the code used to develop AI models publicly available, fostering an open and transparent scientific community and encouraging collaboration for advancing AI research.

Finally, standardising sample collection and image digitisation is crucial to bolster the validity of research involving ML models. This entails rigorously reporting metrics of model performance, such as sensitivity, specificity, accuracy, and other pertinent parameters. By ensuring a consistent reporting practice, researchers can establish a uniform and comparable basis for evaluating findings across studies, thus enhancing the reliability and reproducibility of research outcomes.

*7.3 Explainability Challenge*

To provide actionable and trustworthy outputs, AI models are required to provide transparent and understandable algorithms so that end users can significantly interpret predictive models. Unfortunately, most modern AI models are so complex that providing a good understanding of their decision process becomes difficult. However, a lot of research effort is directed towards explainable AI (XAI).93 This involves using model-agnostic post-hoc methods, such as Shapley values or LIME, to infer which segments of the data drove the decision-making process. Alternatively, model-specific methods like gradient-based methods as GradCAM and its variants can be employed to highlight crucial data segments. Moreover, providing counterfactual hypotheses is another avenue explored in this pursuit. Currently, no golden bullet is available to provide an interpretation of the inner processes of AI models. However, explainability methods will be essential in accurately interpreting the “black-box” outputs on a case-by-case basis after it has been trained, ultimately supporting patient-centred decisions.94 Explainability techniques will provide a more in-depth comprehension of model decisions, promoting transparency, reliability, and deeper insights into the constructed models.

*7.4 Overconfidence Challenge*

Ideally, any reliable automatic system should provide a high confidence scores for correct results, a low confidence for incorrect results, and an unknown label for out-of-distribution data, i.e., data containing features the system has never encountered or been trained upon.95

However, it is widely acknowledged that AI models often tend to provide excessively high scores regardless of the input data type or the accuracy of the answer, resulting in overconfident predictions.96 Moreover, the unpredictable behaviour of AI models when scoring data outside the training distribution makes clinical application unlikely. Classical approaches in ML to mitigate this effect are either post-hoc calibration,97 or built-in out-of-distribution scoring functions.98,99 More recently, especially in the field of digital pathology, where patch-level scores need to be aggregated in a slide-level score and where patch-level uncertainties need to be aggregated into a slide-level uncertainty, Bayesian methods either embedded in the learning process or employed post-hoc have shown some success in tackling overconfident estimates.100,101

*7.5 Privacy and Ethics Considerations*

Ethical concerns are equally paramount. Data privacy is a major concern due to the use and storage of substantial personal data.102 While anonymization provides reasonable protection, advanced reidentification techniques have emerged, highlighting the need for a more robust data management system based on data decentralization and federated learning.103 Moreover, robust cybersecurity measures are crucial to safeguard data against malicious attacks and hackers. Additionally, avoiding discrimination and bias in AI models based on ethnicity, gender, or socioeconomic status is imperative.104 Typically, data from women or minority groups are underrepresented during the constriction of AI models. Such biases can profoundly impact model validity and, consequently, patient outcomes. For instance, AI models used to classify skin lesions have exhibited high accuracy; however, they are often trained on datasets predominantly composed of white patients, with only a limited representation of black patients, ranging from 5% to 10%.105 Therefore, when these models are tested with images of black patients, their diagnostic accuracy significantly decreases. This discrepancy in accuracy may lead to the detection of skin cancers in black patients at more advanced stages, potentially worsening their prognosis.106 Diversifying training datasets is essential to address these disparities and improve the inclusivity and effectiveness of AI applications in healthcare.

*7.6 Biases in ML*

ML-based prediction models hold promise in improving personalised treatment and outcome prediction in IBD by processing intricate datasets and identifying complex patterns.107 However, some biases remain a challenge, hindering clinical implementation. These biases can be categorised into two main types: human-centric and methodology-centric elements of bias.108

Human-centric biases encompass under-, over-, or misrepresentations of specific patient groups, including the previously mentioned racial, gender, age, and socio-economic biases.

Methodology-centric biases encompass distribution biases, wherein the data used for training the ML model may differ from what is observed in clinical practice or may capture only a portion or time-limited data of relevant features. Furthermore, biases related to the methodology selection, including the appropriateness of the selected model and performance metrics for assessing the disease and outcome, should be considered. Lastly, the data leakage bias, which occurs when unexpected additional information from outside a desired training dataset is improperly used to create the model, should also be addressed.

These challenges emphasize the central role of physicians and researchers in this landscape. They should play an active role in contributing to the development of efficient and reliable AI tools. Moreover, interoperability of AI models with the existing electronic health records and development of specific software and resources will facilitate their integration into the clinical workflow.

**8. Regulatory Issues**

The advent of AI and ML models in IBD management challenges regulatory bodies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), as they currently need AI-specific regulatory frameworks. Before ML is widely adopted in medicine, several critical issues need to be addressed, including defining which ML algorithms require regulation, establishing the necessary evidence for ML-based software as a medical device, creating a submission process for such software, and ensuring that the performance of AI-based medical software can be enhanced without compromising patient safety or model effectiveness.109

A significant challenge arises when many ML models intended for clinical use potentially fall under FDA/EMA regulations as medical devices or clinical decision support software.110,111 This entails a complex clearance process, demanding market comparisons, costly fees, and a time-consuming approval process. Furthermore, the dynamic learning capability of ML, which allows continuous improvement, has yet to be regulated. Regulatory agencies are working on strategies to address "adaptive" algorithms but have refrained from clearing any AI-based software that leverages this feature.112

In contrast to the challenging landscape within the IBD realm, many AI tools for polyp detection and characterization in colonoscopy have entered the global market following stringent regulatory clearance in the US, Europe, and other countries. Several factors may account for this disparity. Firstly, the non-IBD field has witnessed extensive prior research against well-developed key performance indicators, starkly contrasting the relatively limited activities in the IBD domain.113 A persistent challenge lies in defining a gold standard for supervised ML processes, a complexity often encountered in the IBD arena (e.g., assessing inflammation activity). Moreover, the inclusion of IBD patients in clinical testing environments poses greater difficulty compared to non-IBD individuals. Addressing these barriers is crucial for effectively introducing AI tools to benefit patients with IBD.

Standardized guidelines emphasizing rigorous and comprehensive ML trials have gained prominence in recent years to facilitate AI model development, regulation, and clinical use. These include initiatives such as SPIRIT-AI, CONSORT-AI, STARD-AI, and TRIPOD-AI, aiming to provide a structured framework for AI in medicine and enhance transparency and reliability in AI research.114

**9. How Can We Translate AI Into Clinical Practice?**

This review highlights significant potential for using AI to revolutionise IBD practice. It suggests that AI will likely surpass human diagnostic accuracy in the future. However, it is crucial to maintain critical composure and assess whether AI represents an illusion or a promising avenue. Regarding future directions, the imminent application in clinical settings is approaching. The effectiveness and reliability of AI will need to await its availability in the hands of numerous clinicians following regulatory approval and subsequent commercialization.

Simultaneously, it is imperative to ascertain whether incorporating AI under appropriate research frameworks offers additional clinical benefits. Moreover, addressing the risks associated with erroneous medical practices stemming from AI is imperative.

The primary concerns are how healthcare professionals interpret AI predictions and their subsequent accountability. While numerous challenges exist, AI has undoubtedly unlocked the door to personalized medicine. It is now an opportunity to embark on the extensive journey of integrating AI into clinical practice while meticulously identifying its advantages and limitations step-by-step.

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**Figure captions**

**Figure 1. Artificial intelligence in Inflammatory Bowel Disease endoscopy.** This figure illustrates the potential applications of artificial intelligence (AI) in advanced endoscopy. New endoscopic tools, including high-definition white light endoscopy, virtual chromoendoscopy (VCE), probe-based confocal laser endomicroscopy, and endocytoscopy, enable the acquisition of high-quality images. However, challenges persists, including subjectivity, high inter- and intra-observer variability, and the need for experts. AI can address these challenges and holds the potential to improve endoscopic assessment and accurately predict outcomes and response to treatment in Inflammatory Bowel Disease. Representative images obtained through VCE-enabled AI (ResNet-50), Endo-BRAIN UC, and Red Density (Pentax, Japan) are included. Created with ‘BioRender.com’. *Abbreviations: HD, high definition; pCLE, probe-based confocal laser endomicroscopy; VCE, virtual electronic chromoendoscopy; WLE, white-light endoscopy.*

**Figure 2. Artificial intelligence in Inflammatory Bowel Disease histology.** This figure illustrates the potential applications of artificial intelligence (AI) models in histology. Initially, pathologists annotate whole slide images, the foundation of convolutional neural networks (CNNs) for slide segmentation. Through an active learning model leveraging uncertainty calculation, standardised digital tissue annotation is achieved, mitigating the burden and biases associated with human annotation. Histology empowered by AI holds the potential to enhance disease assessment and predict outcomes and responses to treatment in Inflammatory Bowel Disease. Representative class activation maps obtained through a CNN that can detect neutrophils are included. Created with ‘BioRender.com’. *Abbreviations: AI, artificial intelligence; CNN, convolutional neural network; WSI, whole slide image.*

**Figure 3.** **Endo-Histo-OMICs in Inflammatory Bowel Disease.** This figure schematically illustrates the three components of the Endo-Histo-OMIC approach: advanced endoscopy, histology and OMICs. Advanced endoscopy images obtained through virtual electronic chromoendoscopy, endocytoscopy and probe-based confocal laser endomicroscopy are provided. The histology section presents a whole slide image and a multiplex-immunofluorescence image targeting intestinal barrier proteins. OMIC techniques, including genomic, transcriptomic, and metagenomic techniques, are schematically represented. The Endo-Histo-OMIC approach enabled by artificial intelligence holds promise in advancing precision medicine for inflammatory bowel disease. Created with ‘BioRender.com’. *Abbreviations: AI, artificial intelligence; IBD, inflammatory bowel disease.*

**Figure 4. Precision medicine and Endo-Histo-OMIC approach enabled by Artificial Intelligence in Inflammatory Bowel Disease.** The comprehensive integration of clinical data, laboratory results, endoscopy, histology, and OMICs through artificial intelligence (AI) models holds the promise of enabling precision medicine for Inflammatory Bowel Disease (IBD). This approach could revolutionise patient profiling, facilitate early diagnosis, explore new biomarkers, predict outcomes and personalise treatments. A shift from a one-fits-all treatment approach to an AI-assisted personalised treatment would mark a revolutionary change in IBD care. Created with ‘BioRender.com’. *Abbreviations: AI, artificial intelligence.*

**Figure 5. Challenges and potential solutions for implementing Artificial Intelligence in Inflammatory Bowel Disease.** This figure outlines the primary challenges of applying artificial intelligence (AI) in Inflammatory Bowel Disease on the left side. On the right side, potential solutions aimed at enhancing and expediting the application of AI are presented. Created with ‘BioRender.com’.