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Beyond the gut: a multidimensional exploration of ulcerative colitis through advanced models, biomarker-driven diagnostics, and artificial intelligence-driven insights

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Abstract

Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease that causes inflammation of the mucosa in the colon and rectum and is the result of a combination of immune dysfunction, genetic susceptibility, environment and lifestyle. Recently, disease diagnosis, prognosis and treatment have been enhanced by recent advances in the integration of artificial intelligence (AI), multi-omics approaches and experimental models. Deep-learning algorithms, such as convolutional neural networks and ResNemodels, are increasingly used for the detection of lesions and automated endoscopic severity assessment, based on pre-established severity indexes such as the Mayo Endoscopic Subscore and the Ulcerative Colitis Endoscopic Index of Severity. Using machine learning-based gene selection techniques, diagnostic gene signatures and immune-related biomarkers have been identified; new targets, such as SLC6A14, oncostatin M pathways, fecal calprotectin and gasdermin D, are emerging for disease stratification and treatment monitoring. Experimental models (such as the Muc2-mutant Winnie mouse) can provide clues about the mechanisms of epithelial barrier dysfunction and chronic inflammation to facilitate translational research. The combination of multi-omics data and explainable AI is improving the development of clinical decision support systems focused on disease progression, treatment response and risk of relapse. A literature search was structured using PubMed, Google Scholar and pertinent databases, and the most relevant and clinically important articles from the last 10-15 years were selected, based on methodological quality and clinical significance. To give a clinically grounded perspective, selected observations from an 18-year-old patient with ulcerative colitis are also included, to illustrate the real-world application of these research developments.

Keywords Gastrointestinal inflammation, inflammatory bowel disease, biomarkers, Mayo endoscopic subscore, murine models

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Introduction

Ulcerative colitis (UC) is a mucosal inflammation of the colon and rectum characterized by unremitting inflammation associated with immunological mediation; it is a relapsing/remitting chronic inflammatory bowel disease (IBD). The etiology of UC, though not very well understood, is known to be multifactorial: it occurs as a result of an inappropriate immune response to microbiota present in the intestines of individuals with a genetic predisposition [1]. The regulation of both adaptive and innate immunity is dysfunctional, along with overactivation of Th2 and Th17 cells producing proinflammatory cytokines—interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin (IL)-17, and IL-13—and the loss of protective B cells and regulatory T cells [2]. Environmental factors—in particular, Western diets, pollution, stress and smoking—also affect the disease's onset, progression and relapse [3].

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The multi-omics and artificial intelligence approaches are transforming the treatment of UC, replacing subjective and invasive diagnostic methods with real-time, precise and predictive so-called endo-histo-omics. The endoscopic diagnosis based on AI, convolutional neural networks (CNNs) in particular, may be quickly and objectively employed to assess the activity of the disease and generate automated scores, such as the Mayo Endoscopic Score (MES) and ulcerative colitis endoscopic index of severity (UCEIS), and reduce interobserver variability [4]. State-of-the-art instruments, such as endocytoscopy with AI software (e.g., EndoBRAIN-UC), can be used to conduct noninvasive real-time histologic analysis, while vascular patterns related to mucosal healing can be measured by Red Density score. Potential directions in the future may include prospective validation, regulatory alignment, explainable AI, and real-time video analysis to enable actionable and personalized clinical decisions [5].

Pathophysiology and systemic nature of UC

UC is a chronic, immune-mediated IBD caused by a multifaceted interplay of genetic predisposition, immune dysregulation, external influences and changes in the gut microbiota. UC may also cause serious systemic and extra-intestinal manifestations, apart from the colon, which emphasizes the importance of thorough understanding and treatment [6]. Fig. 1 shows the complex pathophysiology of UC, representing the important elements of the ways mucosal function can be impaired, including luminal shifts, compromised mucous barriers, gut dysbiosis, NETosis, proinflammatory cell death, mitochondrial DNA release, and atypical T-cell responses that underlie chronic inflammation.

Genetic susceptibility

Genetic predisposition is an essential factor that contributes to multifactorial UC as a chronic IBD. Genetic factors are thought to have a 50-60% heritability rate in IBD. IBD has over 200 susceptibility loci, 23 of which are specific to UC, and many others are shared with Crohn's disease (e.g., IL23R, IL12B). Risk genes tend to include the HLA class II region (HLA-DRB1 0103, which is associated with severe disease) and the IL-23/Th17 pathway, causing an excess of an immune response. Genetic variations in genes including ECM1, CDH1, HNF4a and laminin B1 are linked with elevated intestinal permeability that enables bacteria to provoke inflammation.

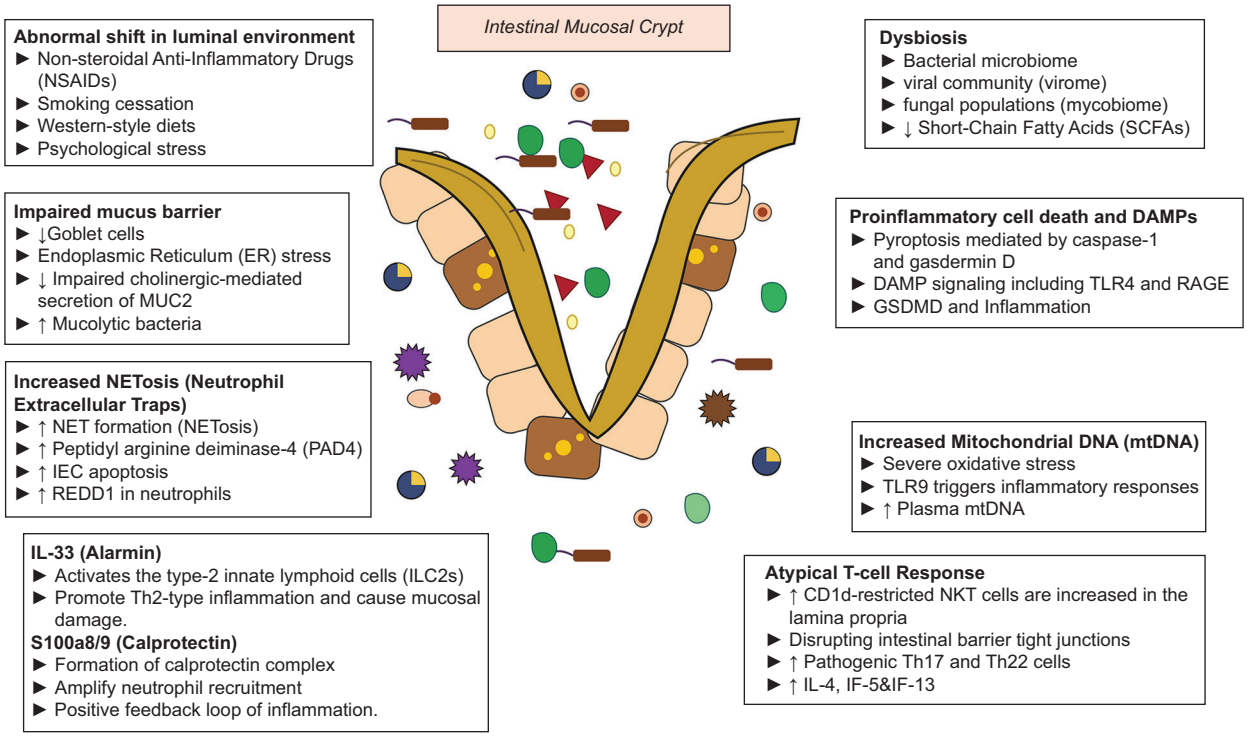


Figure 1 Pathogenesis of ulcerative colitis in the gut mucosa
NSAIDs, nonsteroidal anti-inflammatory drugs; SCFAs, short-chain fatty acids; ER, endoplasmic reticulum; MUC2, mucin 2; NET, neutrophil extracellular trap; NETosis, neutrophil extracellular trap formation; PAD4, peptidyl arginine deiminase-4; IEC, intestinal epithelial cell; REDD1, regulated in development and DNA damage responses 1; IL-33, interleukin-33; ILC2s, type-2 innate lymphoid cells; Th2, T helper 2; S100a8/9, S100 calcium-binding proteins A8 and A9; DAMPs, damage-associated molecular patterns; TLR4, toll-like receptor 4; RAGE, receptor for advanced glycation end products; GSDMD, gasdermin D; mtDNA, mitochondrial DNA; TLR9, toll-like receptor 9; NKT, natural killer T; Th17, T helper 17; Th22, T helper 22; IL-4, interleukin-4; IF-5, a likely typographical error for IL-5, interleukin-5; IF-13, a likely typographical error for IL-13, interleukin-13

In uncommon instances, pediatric onset UC is severe, because single-gene defects (e.g., IL10, IL10RA, IL10RB) result in total immune incapacity [7].

Dysregulation in the immune system

Immune dysregulation in UC is a derangement of the delicate balance between the gut mucosa, microbiota and host immune responses, leading to chronic inflammation that does not resolve [8]. Such imbalance is not restricted to single immune pathways, but is generated by complex, bidirectional interactions of microbial signals, epithelial barrier integrity, and environmental factors and host genetic susceptibility [9]. One of the hallmarks of UC is the breakdown of immune tolerance to commensal microbiota and the subsequent development of chronic relapsing mucosal injury [10]. Pathogenic T-cell differentiation is stimulated by the activation of innate cells to promote antigen presentation and cytokine secretion [11]. This leads to overproduction of pro-inflammatory cytokines, such as TNF-α, IL-6, IL-17, IFN-γ and IL-13, that promote epithelial damage, barrier disruption and perpetuation of mucosal inflammation [12].

Importantly, in UC there is interaction between immune dysregulation, gut dysbiosis and environmental factors [13]. Under normal conditions, short-chain fatty acids (SCFAs) support regulatory immune pathways, but their lack leads to a decrease in the function of regulatory T cells (Treg) and an increase in proinflammatory Th17 responses [14]. There is a numerical expansion of Tregs in the mucosa of UC patients, but these cells are only about 60% functional, meaning they cannot dampen excessive immune activation [15].

For instance, low dietary fiber levels result in decreased production of SCFA; some medications change the microbial profile to have proinflammatory characteristics, which in turn will indirectly increase immune activation [16]. The cross-domain interactions suggest that the immune dysregulation in UC is not a standalone event, but rather a systems-level dysregulation involving microbiota, metabolism and host immunity [17]. There is potential for targeted biologics (anti-TNF, anti-IL-17 therapies), microbiota-directed interventions, and individualized dietary strategies to be personalized to the individual patient's immune and microbiota profile [18].

Environmental and lifestyle factors: dose–response and gene–environment interactions (G×E)

Environmental and lifestyle factors within a complex G×E network drive the onset, progression and relapse of UC [19]. The process of westernization, with respect to diet, pollution, occupation and hygiene practices, is a major multifactorial factor in the emergence of disease and human phenotypic heterogeneity. It is especially important to emphasize that environmental factors are relevant to personalized care; the same environmental exposure can have completely different clinical effects depending on an individual's genetic susceptibility profile, microbiota composition and the ontogeny of immunity [20].

Dietary pattern-dependent effects and dose–response relationships

High intakes of ultra-processed food, refined carbohydrates, simple sugars and trans fats are clearly linked to UC risk and severity in the western diet [21]. Prospective cohort studies show that high intakes of linoleic acid (>10% of total energy intake) are associated with higher levels of disease activity and relapse rates. Dose-dependent relationships were seen with red meat consumption (higher consumption >4 servings per week is associated with 1.5-2.0-fold higher risk of relapse, similar to processed red meat). Conversely, foods containing high amounts of dietary fiber (>25 g/day) and polyphenols have protective effects through various mechanisms: (1) an increase in the production of SCFAs, especially butyrate [20]; (2) anti-inflammatory effects directly mediated by their activation of the aryl hydrocarbon receptor [22]; and (3) selective enrichment of beneficial *Faecalibacterium prausnitzii* and *Roseburia* spp., which are important short-chain fatty acids (SCFAs)-producing bacteria that are depleted in UC [22]. The protective dose appears to be patient-dependent, as a plateau effect is observed at intakes exceeding 30 g/day of fiber, indicating the need for individual dietary interventions based on the baseline level of dysbiosis and the capacity of each individual to produce SCFAs [23].

Sulfur-rich foods and sulfate-reducing bacteria

Foods high in sulfur (cruciferous vegetables, garlic, onions), and some medications such as sulfasalazine, have a paradoxical gene–environment interaction [24]. Sulfur compounds are naturally anti-inflammatory, but whilst they promote anti-inflammatory processes, through glutathione synthesis and oxidative stress mitigation, when taken in excess they can lead to the overgrowth of sulfate reducing bacteria (SRB) (such as *Desulfovibrio* spp.) which produce hydrogen sulfide (H_2S) a mucosally-toxic byproduct, that can damage the tight junctions of intestinal epithelium and worsen barrier dysfunction [25]. This phenotype is more evident in genetically susceptible persons with genetic variants of CDH1 or ECM1 mutations that increase intestinal permeability. Shotgun metagenomics should be considered in personalized nutritional counseling to determine if there is an SRB predominance. On the other hand, if the microbial diversity is well preserved, a standard application of cruciferous vegetables containing fiber may be well tolerated [26].

Smoking paradox and nicotine–immune interactions

The apparent protective effect of cigarette smoking on UC incidence and severity is a dramatic illustration of how environmental factors affect host immunity in ways that are opposite to conventional expectations. Smoking is consistently

associated with a lower incidence of UC (40-60%) and smaller relapse rates (30-50%), a time-dependent association that discounts the likelihood of confounding [27]. Nicotine modulates immune responses structurally, via α7 nicotinic acetylcholine receptors (α7nAChR) on immune cells, such as macrophages and T lymphocytes, and consequently shifts the equilibrium from proinflammatory Th1/Th17 to Th2/Treg dominant phenotypes. Nicotine also decreases intestinal permeability by increasing the expression of claudin-2 and the tightness of tight junctions [28]. Nicotine replacement therapy (transdermal nicotine patches, oral nicotine) has been studied in some clinical trials, with variable effectiveness [29]; in genetically susceptible individuals with risk alleles to IL23R, who show an exaggerated Th17 response to perturbation, this approach has been considered. Based on current evidence, the use of nicotine replacement is not recommended as a primary treatment for asthma, but is potentially indicated as an adjunctive immunomodulatory treatment in very specific cases with steroid-refractory disease, a genetic predisposition for the α7nAChR pathway, and failure to tolerate biologic treatment [29].

Psychological stress, intestinal barrier function, and the microbiota–gut–brain axis

Psychological stress and anxiety lead to a chronic increase in circulating corticotropin-releasing hormone, which leads to hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis and increased glucocorticoid signaling. Several mechanisms contribute to proinflammatory immune skewing during chronic stress-induced glucocorticoid dysregulation: (1) long-term exposure to corticotropin-releasing hormone directly skews immune cells toward-Th1/Th17 polarization; (2) impaired negative feedback on the HPA axis increases the likelihood of cortisol resistance in immune cells, thereby decreasing anti-inflammatory signaling; and (3) stress-induced sympathetic nervous system activation due to increased blood levels of norepinephrine promotes the recruitment of inflammatory monocytes and polarization of Th17 [30]. In addition, chronic stress causes zonula occludens-1 (ZO-1) dysregulation and alters the protein structure of claudins, the tight junction proteins, increasing the intestinal permeability which allows bacteria to be translocated and antigens to be sampled. Critically, these stress-induced perturbations directly affect microbial community structure; stress results in an increase in *Proteobacteria* and decrease in *Firmicutes* leading to a proinflammatory dysbiotic phenotype. Psychogastroenterology interventions like Post-Traumatic Stress Disorder Mindfulness-based interventions, cognitive behavioral therapy (CBT), and gut-directed hypnotherapy (GDH) demonstrate clinically significant improvements in UC, comparable to those seen with mesalamine monotherapy, especially in patients with documented stress-reactive dysbiosis (elevated levels of fecal LPS-binding protein [LBP], or serum LPS, markers of translocation), and identified HPA axis dysfunction [31].

Gut dysbiosis: mechanistic interplay with immune dysregulation, environmental perturbations, and therapeutic implications

The gut dysbiosis seen in UC is not just a matter of microbial imbalance, but a multifaceted imbalance of host–microbiota homeostasis in the setting of genetic susceptibility, environmental triggers and immune dysfunction. This state features lower microbial diversity, lower numbers of beneficial bacteria, including the butyrate-producing *Faecalibacterium prausnitzii* and *Roseburia* species, and increased numbers of proinflammatory bacteria, such as Proteobacteria and adherent-invasive *Escherichia coli* (AIEC) [32].

Mechanism I: SCFA-mediated barrier dysfunction and immune dysregulation

SCFAs are important for colonocyte energy metabolism and epithelial integrity, with butyrate being the most critical. In UC, the loss of SCFA-producing bacteria reduces butyrate availability, which impairs mitochondrial β-oxidation and starves the colonocytes. This cellular energy deficit subsequently disrupts tight junction proteins—such as claudin-1 and occludin—compromising their structural integrity and increasing intestinal permeability. In addition, butyrate acts as a histone deacetylase inhibitor, enhancing the expression of Foxp3 to induce regulatory T (Treg) cell differentiation, thereby promoting the immune system's ability to develop immune tolerance [33].

Mechanism II: environmental factor–dysbiosis–immune axis

Dysbiosis is caused by different types of medication, including nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics and proton-pump inhibitors (PPIs). NSAIDs are useful in suppressing protective prostaglandins and promoting the growth of harmful bacteria. PPIs increase the gastric acidity, which will lead to an overgrowth of Proteobacteria and make the person more susceptible to infection by *Clostridioides difficile*. Diet and psychological stress further alter microbiota composition and immune responses, exaggerating disease severity [34].

Mechanism III: dysbiosis-driven pathobiont expansion and immune activation

Dysbiosis leads to an increase in the number of pathobionts, such as AIEC and *Ruminococcus gnavus*, that secrete inflammatory molecules, such as lipopolysaccharides and flagellin. These elicit immune responses via pattern recognition receptors that involve the activation of Th1 and Th17. AIEC has the ability to colonize epithelial cells and macrophages and to perpetuate chronic inflammation. Furthermore, a molecular mimicry of bacterial and host antigens can interfere with immune tolerance mechanisms, leading to a further worsening of the disease process [33, 34].

Therapeutic implications and personalized interventions

Prebiotics (inulin, resistant starch) can help to replenish beneficial bacteria, and probiotics and symbiotics can maintain the balance of microorganisms [29]. Fecal microbiota transplantation (FMT) has moderate efficacy, and is especially effective in the treatment of patients with severe dysbiosis [32]. Microbial composition is influenced by dietary strategies, in particular so-called "Mediterranean" diets that are rich in fiber and polyphenols, and these help to lower inflammation. A promising future strategy for UC management would be personalized interventions that use microbiota profiling and dietary changes [34].

Systemic reactions

UC is an immune-mediated disease, which is chronic predominantly in the colon, and the systemic inflammation in UC can lead to severe extraintestinal manifestations in as many as 30 percent of patients. They normally include peripheral arthritis, skin rash (erythema nodosum or pyoderma gangrenosum), eye inflammation (episcleritis, scleritis), and fatigue. Pyoderma gangrenosum is less common, but more severe. UC is linked to such conditions as episcleritis, and more severe manifestations of uveitis or scleritis that can lead to the loss of vision [34]. Primary sclerosing cholangitis is a potentially severe progressive liver disease that is associated with UC, and is typically associated with fatigue and jaundice. The resultant effect of the chronic inflammation may include deep fatigue, thromboembolism or anemia [35].

Internal hemorrhoids are encountered more frequently in patients with active colitis, attributed to chronic straining during episodes of diarrhea, increased anorectal venous congestion and prolonged tenesmus [36]. Patients with active UC proctitis often have congested, prolapsing internal hemorrhoidal mucosal folds, as in the case shown in Fig. 2 (endoscopic view of the anal canal and distal rectum).

AI to assess endoscopy

The use of AI, and specifically deep learning and CNNs, in the field of UC assessment has been considered as a promising approach; however, it is limited by several key factors that need to be thoroughly investigated [37]. In the controlled setting, some AI systems have also been shown to be >90% sensitive and specific—even more sensitive than, or similar to expert endoscopists—and this apparent superiority needs to be carefully considered [38]. Performance is highly data- and task-specific, and data can also impact performance, as models can only be tested on other sets of data that are unrelated to their training, and this can often reduce accuracy by 10-25%. AI algorithms perform at roughly the same level as clinicians in controlled settings, but their generalization to different endoscopic platforms (Olympus vs. Fujifilm vs. Pentax systems),



Figure 2 Endoscopic view of the anal canal and distal rectum showing congested, prolapsing internal hemorrhoidal mucosal ulcerative colitis proctitis

to different image quality and to different disease phenotypes has not been fully validated [39]. In addition, there is no mention of the interobserver variability between these various AI systems in most publications, indicating that, rather than doing away with subjectivity, the use of algorithmic subjectivity may simply move the source of bias from human to algorithmic, unless there is robust external validation in truly independent, multicenter cohorts with varied patient populations [40]. Table 1 summarizes the major deep learning and machine learning algorithms used for automated endoscopic scoring, disease severity assessment and dysplasia detection.

Opportunities and limitations of deep learning for endoscopic imaging

Early deep learning models, such as ResNet-152 and Vision Transformers, have shown good results in endoscopic image classification, but there are important challenges to be addressed [61]. The prediction of MES by CNNs has been externally validated, with an accuracy of 82-89% in prospective studies, and 85-92% for the UCEIS [62]. But performance on external test sets from other institutions or endoscopy platforms can drop by 10-25%, showing significant generalization errors that prevent its use in clinical practice [63]. The spatiotemporal transformer models show greater consistency than classical CNNs (accuracy retention of 88-94% on external data vs. 65-78% for CNNs), by considering the dynamics of the disease over the different frames of a video [64]. The architectural benefit brings a high computational penalty, making it hard to access in low-resource environments. Multimodal integration approaches that combine white-light endoscopy with endocytoscopy, or endoscopy with narrow-band imaging, are promising; vision-language models such as VIGIL have an

Table 1 AI approaches for endoscopic assessment in UC

AI approach	Model examples	Clinical application & key advantage	References
CNN-based models	ResNet, DenseNet, Inception V3	High accuracy (88-97%) in the detection of inflammation to differentiate between MES or UCEIS categories	[41]
Transformer models	Vision Transformers, Video Transformers, Arges	Multi-frame and video-based evaluation with less interobserver variation and spatiotemporal analysis of endoscopy	[42]
Multimodal AI	VIGIL, multimodal fusion networks	Forecasts histological recovery (AUC=0.94) with the combination of WLE, endocytoscopy, clinical data, and biomarker	[43]
Machine learning	RF, SVM, XGBoost, MLP	Prediction of disease, relapses, and therapy response to allow individual patient treatment planning	[44]
Ranking-CNN	UCEGS (Ulcerative Colitis Endoscopic Gradation Scale)	Strong correlation with MES (>0.89) and better monitoring of fine-grained severity scoring.	[45]
Vision-language models	CLIP-based medical models, Med-PaLM-M	Combines endoscopic images with clinical text reports for automated reporting, severity grading, and decision support	[46]
Foundation medical models	Med-PaLM, BioGPT, GPT-based clinical AI	Support in clinical decision-making, recommendations on treatment based on guidelines, and background reports of UC patients	[47]
Video-AI for endoscopy	Temporal CNN-Transformers, EndoViT	Live scoring of colonoscopy, automated prediction by MES/UCEIS, and enhanced inter-center reliability	[48]
Radiomics-AI	CNN-radiomics, LASSO radiomics	Utilizes CT/MRI radiomic characteristics to assess inflammation and provide an indication of treatment response as a noninvasive technique	[49]
Multi-omics AI	Deep neural networks, autoencoders	Integrates genomics, microbiome, proteomics and transcriptomics for precision medicine and prognosis prediction	[50]
Explainable AI (xAI)	Grad-CAM, SHAP, LIME	Improves clinician trust by visualizing inflamed regions and explaining model predictions	[51]
NLP on electronic health records	ClinicalBERT, BioBERT	Derives history of flares, medication response and disease severity out of electronic health records	[52]
Federated learning	Multi-center federated CNN/transformers	Allows privacy-aware training on a hospital-wide basis, and enhances the generalizability of UC models	[53]
Reinforcement learning	Treatment-policy optimization models	Recommends the best biologic or steroid sequencing depending on the patient's response pattern	[54]
Digital twin models	Patient-specific simulation AI	Generates simulated UC patients in order to replicate the progression of the disease and to optimize therapy plans	[55]
Graph neural networks	Patient–drug–disease networks	Discovers the best treatments and forecasts reaction with network-based precision medicine	[56]
Capsule endoscopy AI	CNN video models	Detection of inflammation and ulcers in capsule endoscopy images in an automated fashion	[57]
Wearable & remote monitoring AI (latest)	Time-series deep learning models	Early intervention of flares through wearable data, symptoms and home biomarkers prediction	[58]
Predictive outcome AI	DeepSurv, Cox-DL	Forecasts long-term outcomes, colectomy risk and hospitalization	[59]
Robotic endoscopy AI	AI-assisted robotic colonoscopy systems	Enhances lesion identification, orientation and real-time evaluation of mucosa	[60]

AI, artificial intelligence; UC, ulcerative colitis; MES, Mayo endoscopic score; UCEIS, ulcerative colitis endoscopic index of severity; CNN, convolutional neural network; WLE, white-light endoscopy; AUC, area under the curve; LASSO, least absolute shrinkage and selection operator; NLP, natural language processing

accuracy of 91% for predicting histological healing in carefully selected validation cohorts [65]. These models, however, have not been prospectively validated in independent multicenter cohorts, and critical health economic analyses that prove cost-effectiveness are absent from the literature [66]. Explainable AI techniques (attention maps, saliency mapping, Grad-CAM, Integrated Grad Indeps) offer some mechanistic transparency, but these techniques are poorly leveraged in published validation studies, and their clinical reliability is only poorly characterized [66]. A major challenge for a robust generalized model is data heterogeneity, which has been observed to result from different image preprocessing, different techniques used by the endoscopist, and also the representation of the disease severity [67].

Clinical data integration and machine learning

The promise of integrating endoscopic imaging with electronic health records and biomarker data is an exciting, but technically and interpretatively challenging concept [68]. In retrospective studies, machine learning classifiers (random forest, support vector machine, multilayer perceptron) have been able to identify UC phenotypes compared to other IBDs with between 78% and 88% accuracy [68]. However, there is significant variation in published studies with respect to patient selection, the spectrum of disease stages represented, missing data treatment, approach to feature selection, and external validation procedures—to name but a few—which reduces the generalizability of results [69]. Pooled sensitivities (85-92%) and specificities (81-89%) for detection of mucosal healing from meta-analyses are highly variable across datasets, with an accuracy ranging from 72-96% [69].

AI endoscopic automated scoring systems: addressing interobserver variability without introducing new biases

The use of AI-based automated scoring systems solves a real clinical issue (objections due to interobserver variability within categorical inflammation scores such as MES or UCEIS), while adding extra complexities [62]. Video colonoscopy computer-aided detection systems have obtained kappa coefficients of κ=0.844 (MES) and κ=0.855 (UCEIS) in comparison to the expert consensus, with similar or slightly higher interobserver agreement (κ=0.78-0.82 for human experts) [63]

Recent model architectures integrate 10-point scales of inflammation, including ranking CNNs, offering numerical granularity as opposed to the traditional categorical MES scores [62]. In theory, this will offer a more accurate representation of disease heterogeneity, but clinical evidence demonstrating that continuous scoring would lead to better therapeutic decisions or disease prevention in the absence of disease flares is lacking. Spatial heterogeneity in mucosal inflammation is observed, especially at the boundaries between different segments of the colon, and could be considered as a theoretical analytical benefit of AI systems that analyze multiple sequential frames [63]. Fig. 3 shows endoscopic images of the inflammatory gradient from the normal proximal colon (left 2 images: intact haustral folds, preserved vascular pattern) to the inflamed distal segment (right 2 images: erythema, erosions, mucopus).

Explainable AI in clinical practice: building trust through mechanistic transparency

In clinical use, the use of explainable AI (xAI) approaches, such as attention mechanisms, saliency mapping and gradient-based models (Grad-CAM, Integrated Gradients, Layer-wise Relevance Propagation), is of paramount importance to verify that AI models are able to detect biologically relevant aspects of a tissue, such as mucosal erosions, vascular loss and crypt irregularity, and not spurious features of an image or quality markers. New architectures, such as ResNet-152, DenseNet-201, Vision Transformers and Swin Transformers, have achieved better results on the internal validation set [61], but head-to-head comparison of the accuracy of clinicians with accuracy of models (with and without xAI visualization) in real clinical settings is still limited. Traditional deployment strategies are pragmatic, measuring model uncertainty and designing human-AI workflows that involve sending low-confidence predictions to a human expert for review; such multilevel strategies need to be formally validated in prospective studies [65].

Multi-omics approaches in UC: complexity without established clinical translation

Multi-omics integration of genomics, transcriptomics, proteomics, metabolomics and microbiomics gives a comprehensive molecular characterization of UC pathogenesis [69]. However, converting these signatures to clinically useful biomolecules or individual treatment plans presents significant challenges [67]. Although multi-omics

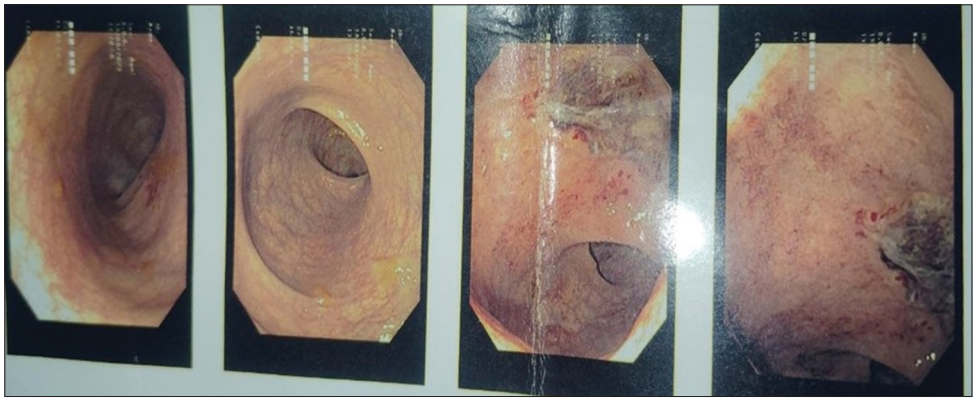


Figure 3 Sequential endoscopic images showing the inflammatory gradient from a normal proximal colon to an inflamed distal segment in ulcerative colitis

approaches conceptually could capture complex host genetic, immune system and dysbiosis interactions, they have not yet been validated in prospective multicenter studies, have not yet been clearly defined by clinical decision thresholds that approximate clinically informative findings from incidental findings and, most critically, do not have evidence supporting their added clinical value in comparison to traditional clinical parameters and traditional biomarkers [66].

Gene signatures and transcriptomics: from correlation to causation

A dysregulated network of genes related to barrier function genes and immune genes is consistently shown in the transcriptomic analyses of inflamed vs. non-inflamed UC mucosa [69]. Gene signatures of increased expression of proinflammatory mediators (IL-6, IL-17, TNF-α, IL-23) and decreased expression of barrier-function genes (claudins, occludin, ZO-1) have been identified by machine learning stratification techniques, using high retrospective predictive accuracy [69]. The main limitations that hamper translational applications are: (1) most published transcriptomic studies are single-center, with low sample sizes (n=20-80 patients), and not powered independently for reliable gene discovery; (2) only a fraction of these studies have independent prospective validation cohorts, and validation cohorts are often considerably less statistically powerful than discovery cohorts; (3) most discovered signatures lack functional validation—e.g., gene editing or pharmacologic manipulation, in appropriate model systems, to demonstrate that targeted gene modulation improves disease outcomes; (4) There is no evidence that transcriptomic signatures add predictive power to treatment response beyond that provided by clinical phenotyping alone. Therefore, transcriptomic signatures should be viewed as correlative markers, which offer mechanistic hypotheses but cannot be considered as diagnostic or prognostic markers. The specific loci identified in genome-wide association study (GWAS) for UC susceptibility (such as IL23R, JAK2 and STAT3) exhibit strong genetic associations with susceptibility to UC, show weak individual effect sizes, and have not been validated for clinical utility in predicting individual treatment response [69].

Proteomics and metabolomics: mechanistic insights without clinical validation

Proteomic and metabolomic profiling reveal functional derangements in UC, including dysregulated inflammatory proteins (calprotectin, lactoferrin, lipocalin-2), altered mucus glycosylation, and disrupted metabolic pathways (tryptophan metabolism, SCFA production). Integration with transcriptomics and microbiome data provides multilevel systems understanding [70].

Technical standardization remains problematic: sample collection protocols, sample storage conditions, analytical platforms (mass spectrometry variants, protein arrays, metabolomic platforms) introduce substantial variability, complicating clinical translation [71]. Costs of comprehensive proteomic and metabolomic analysis ($500-$2000 per patient) remain prohibitive for routine clinical practice, without demonstrated cost-effectiveness [72]. While AI integration with these multimodal datasets theoretically could enhance predictive power, prospective intervention trials demonstrating this superiority are notably absent [73]. Noninvasive biomarkers (serum or fecal proteins, such as fecal SLC6A14 expression) would be clinically desirable, but require rigorous prospective validation in independent cohorts, to demonstrate that these biomarkers predict treatment response and patient outcomes better than existing clinical markers, before their incorporation into precision-medicine workflows [74].

Microbiome integration: correlation with disease without established causation or therapeutic predictive value

Metabolomic and proteomic profiling uncovers functional dysregulations in UC, such as deranged inflammatory players (calprotectin, lactoferrin, lipocalin-2), impaired mucous glycosylation and altered metabolism (tryptophan metabolism, SCFAs) [75]. Multi-level systems understanding is achieved through the integration of transcriptomics and microbiome data [76]. There are still several important gaps, however: only a few prospective studies have examined the ability of identified proteomic or metabolomic markers to stratify patients *a priori* into subgroups with a meaningful difference in clinical outcome compared to standard-of-care strategies [77]. Technical standardization remains a significant hurdle: sample collection protocols, storage conditions, and analytical platforms—including mass spectrometry variants, protein arrays, and metabolomic platforms—exhibit high variability, leading to difficulties in clinical translation [78]. Comprehensive proteomic and metabolomic analysis of a patient (500-2000$ per patient) is not sufficiently cost-effective for clinical use in routine practice [79]. Theoretically, AI integration with these multimodal datasets could boost the predictive power, but there are no prospective intervention trials that have shown this advantage [80]. Ideally, noninvasive biomarkers (e.g., serum or fecal proteins, such as expression of SLC6A14 in the stool) would be valuable, but could only be incorporated into precision-medicine workflows if treatment response and patient outcomes are better predicted by these proteins than by currently available clinical markers, after prospective validation in independent patient cohorts [81].

Emerging biomarkers for stratification and monitoring

The "treat-to-target" approach in UC emphasizes objective inflammation measurement and titration towards clinical, endoscopic and histologic remission [82]. New biomarkers (serum, stool, molecular) should be explored for noninvasive use. Biomarkers need to meet stringent criteria for clinical incorporation: (i) prospective validation in independent

multicenter cohorts; (ii) cost-effective biomarker-guided treatment adjustment compared with established markers in predicting clinical outcomes (e.g., fecal calprotectin: sensitivity 74-97%, specificity 71-94%; C-reactive protein: sensitivity 59-85%, specificity 73-95%) [83]; (iii) comprehensive health economic analysis showing cost-effectiveness; and (iv) prospective controlled trials demonstrating that biomarker-guided treatment adjustment is superior to standard treatment in improving outcomes. Although there is a large amount of biomarker research going on, these requirements get overlooked by publications, which often leads to publication bias and overestimates the clinical relevance in high impact journals. Table 2 highlights novel serum, fecal and imaging biomarkers, including anti-integrin α vβ6 autoantibodies, oncostatin M, calprotectin neo-epitopes (CPa9-HNE), gasdermin D, and others that enhance diagnostic accuracy and treatment response prediction.

Experimental and preclinical models in UC

Murine models and complementary experimental systems in UC pathogenesis

Murine models play crucial roles in the study of UC pathogenesis, and recapitulate many human pathophysiological features of the disease, such as epithelial barrier dysfunction, immune dysregulation and chronic mucosal inflammation. Winnie mice carry mutations in the *muc2 gene* that encodes the main structural mucin, and develop mucus layer thinning and chronically inflamed intestines, providing a mechanistic approach towards understanding the role of an intact mucus barrier, immune responses and interactions with gut microbiota [95]. The Winnie model experimental capabilities are greatly enhanced by complementary systems: (1) in Dextran Sulfate Sodium-induced colitis models, acute inflammation and chronic inflammation both respond to pharmacologic and immunologic treatment, with kinetics and reversibility different from Winnie spontaneous disease; (2) IL-10 knockout models demonstrate the progression of Th1 mediated colitis; (3) T-bet/Rag2 double-knockout models show bacterial antigen-driven immune responses; (4) STAT3-deficient intestinal epithelial cell models show cell-autonomous barrier dysfunction; and (5) humanized microbiota models using human fecal communities elucidate microbiota-driven pathogenesis. Overall, these complementary models reveal several mechanistic pathways that are all involved in UC heterogeneity, and that account for variability in treatment response: barrier dysfunction (Winnie model), innate immune activation (DSS model), adaptive immunity (IL-10 knockout model) and microbial dysbiosis (humanized microbiota model) [96].

Table 2 Key emerging biomarkers for stratification and monitoring in UC

Biomarker	Description & clinical significance	References
Anti-integrin αvβ6 autoantibodies	UC serum biomarker that has a high specificity (96%) and can help to differentiate between UC and irritable bowel syndrome, as well as predict the onset of UC up to 10 years prior to the emergence of symptoms	[84]
Leucine-rich alpha-2 glycoprotein (LRG)	Circulating inflammatory protein was closely linked with disease activity and it assisted in the identification of mucosal healing especially among anti-TNF-treated patients and CRP is suppressible	[85]
Serum oncostatin M (OSM)	Pro-inflammatory cytokine the increased baseline levels of which suggest the absence of response to anti-TNF/anti-integrin (vedolizumab) treatment and poor prognosis	[86]
Calprotectin neo-epitope (CPa9-HNE)	Specific calprotectin fragment that is an active neutrophil inflammation with high diagnostic values (AUC of 0.96) to discriminate between UC and healthy controls	[87]
Gasdermin D (GSDMD)	Inflammatory cell-death protein whose AUC is good (~0.97) to identify cases of moderate-to-severe disease and reflect the existence of an inflammatory process	[88]
Trefoil Factor 3 (TFF3), serum amyloid A (SAA)	Novel serum biomarkers that could be more predictive of full mucosal healing and inflammatory conditions than the traditional CRP	[89]
Fecal MMP-8, MMP-12	Matrix metalloproteinases are associated with tissue inflammation that may correlate strongly with disease activity and complement or outperform fecal calprotectin in some settings	[90]
Fecal calprotectin	One of the most popular noninvasive stool markers linked to mucosal inflammation and endoscopic disease activity	[91]
NAR (neutrophil-to-albumin ratio), CAR (CRP-to-albumin ratio)	Simplified and easy blood-based indices applicable in the determination of responsiveness to and prognosis of treatment, particularly in infliximab-treated patients	[92]
SAA, IL-6, IL-8, eotaxin-1 combinations	Multi-marker inflammatory panels that boost prediction of the endoscopic activity and severity of the disease over single biomarkers	[93]
Multi-biomarker+AI models	Combine serum, fecal and imaging biomarkers with machine learning to improve disease stratification, predictive of relapse and tailored therapy selection in UC	[94]

UC, ulcerative colitis; TNF, tumor necrosis factor; CRP, C-reactive protein; AUC, area under the curve

Translational drug development: from mechanism to clinical proof of concept

Preclinical animal models play a crucial role in translating molecular findings into clinical practice, by providing experimental evidence for the efficacy of new therapeutics. By testing investigational drugs and biologics in relevant murine models, researchers can interrogate their mechanism of action and therapeutic potential relative to proinflammatory mediators (e.g., TNF-α inhibitor, IL-23 neutralizing antibodies), restorative pathways (e.g., growth factor signaling), or immune checkpoint targets (e.g., JAK inhibition, integrin antagonism). Notable examples of therapeutics validated in animal models of UC include: (1) anti-TNF monoclonal antibodies (e.g., infliximab, adalimumab), which were developed based on preclinical studies demonstrating the pathogenic role of TNF-α in DSS and IL-10 knockout models, and are effective first-line treatments for UC, with response rates of 40-50% in induction studies; (2) the anti-integrin monoclonal antibody vedolizumab, which was discovered in mouse models of UC by targeting α4β7 integrin and achieves response rates of 25-30% in clinical trials; (3) JAK inhibitors (e.g., tofacitinib) under investigation for IBD, which were based on mechanistic studies of STAT3 signaling in IL-10 knockout mice and demonstrate objective response rates of 40-45% in UC clinical trials [97]. Animal models contribute to clinical development by enabling safety assessment, determining optimal dosing regimens, and elucidating mechanisms of action in preparation for first-in-human studies. Accelerating the development of individualized treatment modalities for UC requires careful assessment of whether basic science discoveries have clinical relevance and predictive value for treatment response, which necessitates extensive preclinical experimentation as well as prospective clinical validation [98].

Explainable AI and integrated data systems

One of the key challenges in precision medicine for UC is to combine various omics and clinical data to predict clinical response to treatment or risks of flares in individual patients. To overcome this, integrated data systems integrate multi-omics (genomic, proteomic and microbiome), clinical, laboratory, imaging, and electronic health record (EHR) data into patient profiles that help to capture the biology of the disease and the variability between patients [99]. Explainable AI (xAI) helps these systems to produce explainable results, demonstrating to the clinician which factors have contributed to the prediction, e.g., a risk score or a recommended treatment. They can both aid in risk stratification, relapse prediction, treatment selection and identification of diagnostic and prognostic biomarkers. They can also enable continuous monitoring of disease activity, by connecting laboratory, endoscopy and histological data. Transparency in decision support tools can lead to better quality and consistency of care in UC in clinical practice [100].

Concluding remarks

UC is a multifactorial disease, in which a variety of genetic susceptibilities, immune system abnormalities, and environmental factors and changes in gut microbiota all contribute to chronic mucosal inflammation and systemic manifestations. Advances in multi-omics technologies and the discovery of biomarkers are facilitating more accurate disease stratification and more precise monitoring. The use of AI, deep learning and automated endoscopic scoring systems is improving the diagnostic accuracy, objectivity and prediction of treatment response. Together, these innovations are pushing the paradigm of UC management towards the precision-medicine model of individualized, predictive, and effective therapies. While these exciting developments hold great potential, there are still a number of obstacles to the clinical use of AI-powered tools in UC. Some of the challenges are the lack of prospective validation from a variety of patient cohorts, inconsistent datasets, privacy and interoperability issues, and the demand for clinically interpretable (explainable) AI models. Crosstalk between multi-omics and clinical and imaging data for creating disease models at a systems level is also of paramount importance. These integrative strategies, along with technological advancements in computational techniques and regulatory procedures, have great potential to address the current challenges and facilitate truly personalized, data-driven UC management in the future.

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