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Advancing the precision management of inflammatory bowel disease in the era of omics approaches and new technology

Liu XY *et al*. Precision management of IBD

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Abstract

There is great heterogeneity among inflammatory bowel disease (IBD) patients in terms of pathogenesis, clinical manifestation, response to treatment, and prognosis, which requires the individualized and precision management of patients. Many studies have focused on prediction biomarkers and models for assessing IBD disease type, activity, severity, and prognosis. During the era of biologics, how to predict the response and side effects of patients to different treatments and how to quickly recognize the loss of response have also become important topics. Multiomics is a promising area for investigating the complex network of IBD pathogenesis. Integrating numerous amounts of data requires the use of artificial intelligence.

Key Words: Inflammatory bowel diseases; Precision management; Multiomics; Artificial intelligence

Core Tip: Inflammatory bowel diseases (IBDs) exhibit different pathogeneses and clinical manifestations. Making precise and appropriate therapeutic decisions according to the condition of each patient remains challenging. We summarize the clustering

strategies, the approaches used to apply multiomics and artificial intelligence to IBD precision management.

INTRODUCTION

Since it was first proposed in 2011[1], the concept of precision medicine has become increasingly popular and attracted much attention. Great progress has been made, especially in the treatment of cancer. Precision medicine typically refers to the use of targeted therapy based on etiology and mechanism. The essence of the idea involves classifying individuals with common characteristics into the same subgroup using specific clinical features, treatment features and prognoses. Thus, this strategy should actually combine a wide array of data, including clinical, genetic and environmental information, as well as multiple types of biomarkers[2]. These efforts would add to the objectivity and flexibility of treatment decision-making.

Inflammatory bowel disease (IBD) is a group of intestinal disorders of unknown etiology characterized by inflammation that arises from a complex interaction between genetic and environmental factors and immune responses[3]. An increasing number of studies have reported on the great heterogeneity of IBD patients in terms of pathogenesis, clinical manifestation, response to treatment and prognosis, and IBD is currently regarded as a continuous spectrum of diseases[4]. The introduction of biologics has greatly improved the quality of life of IBD patients, which also embodies precision medicine to some extent. However, due to the complexity of pathogenesis, targeting only immune pathways without addressing the genome or microbiome may result in limited success[5]. The treatment strategies used are largely based on evidence from clinical trials, which typically do not stratify patients with enough precision. Additionally, the frequency of treatment may be indicated for a certain population, but this approach might not be the most suitable for an individual. Compared to the oncology field, there is still much room for precision medicine development in IBD.

In this review, we discuss the strategies used to categorize IBD patients and biomarkers for identifying these subgroups. We suggest that applications of multiomics

and artificial intelligence (AI) approaches could facilitate the precision management of IBD patients (Figure 1).

THE HETEROGENEITY OF IBD AND CLUSTERING STRATEGIES FOR IBD PATIENTS

Phenotype refers to the traits that can be observed in patients, and deep phenotyping plays a key role in the progress of precision medicine[2]. In other disease contexts, there is also the concept of endotype, which is defined as the molecular mechanism underlying the visible phenotype[6]. However, clustering phenotypes and endotypes remains difficult in the context of IBD due to heterogeneity.

The Montreal classification is the most widely used clinical classification of IBD and considers age at diagnosis, location and behavioral factors[7]. The characteristics and natural history of IBD seemed to vary depending on the age of onset[8]. Very early onset IBD (VEO-IBD), defined as IBD occurring in those who are diagnosed under the age of 6 years and sometimes exhibiting a more aggressive disease pattern, seemed to have stronger genetic triggers with less environmental influence[9]. In addition, complications or extraintestinal organ involvement can also be used to identify some unique subsets of IBD patients. For example, IBD patients who experienced complications with primary sclerosing cholangitis (PSC) have been shown to exhibit higher rates of colectomy, cancer and death than non-PSC-IBD patients[10]. However, current clinical classification is far from the precise identification of IBD phenotypes.

Some specific genetic factors have been found to determine disease progression, which is difficult to assess by clinical manifestations. Next-generation sequencing has been used to identify more than 100 monogenic causes that could manifest as IBD-like phenotypes. The genes involved in monogenic IBD disorders are generally classified into six categories according to the mechanisms: epithelial barrier defects; T-cell and B-cell defects; hyperinflammatory and autoinflammatory disorders; phagocytic defects; immunoregulation defects; and others[11]. For example, mutations in the IL-10 pathway could lead to neonatal or infantile VEO-IBD with severe enterocolitis and crissum

disease by impairing IL-10-mediated control of inflammatory responses involving IL-1 and IL-23. Mutations in *CYBB* could lead to chronic granulomatous disease characterized by intestinal inflammation and autoimmune disease due to impaired antimicrobial activity caused by defects in NADPH oxidase[12,13]. Conventional treatment in patients with the subsets of IBD that are largely driven by genetic factors often exhibit unsatisfactory efficacy, and these patients have poor prognosis. These various mechanisms that underlie the effects of monogenic mutations also have some crossover with the mechanisms involved in sporadic and multifactorial IBD, which reflects the divergence and convergence of the mechanisms. For precision treatment of IBD, strategies should not be limited to therapies targeting upstream etiology; therapy based on more superficial mechanisms should also be pursued.

The etiology of monogenic causes, which account for only a small percentage of IBD cases, is complex, but sporadic IBD involves many more factors. More than 260 risk loci have been identified to be associated with sporadic IBD by genome-wide association studies (GWASs)[14], yet these loci only explained approximately 20% of the genetic heritability in complex adult-onset IBD[15]. This finding is easy to understand because there are also environmental, microbiota or other factors involved in the pathogenesis of IBD. IBD cannot be classified by a single factor, but the application of biomarkers can aid in the advancement of the precision management of IBD to some extent.

BIOMARKERS

Due to the rising incidence of IBD and the inconvenience of endoscopy, there is an urgent need for noninvasive, accessible and cost-efficient biomarkers. Precision medicine should cover the whole management process of IBD patients, including the early identification of patients at potential risk for disease progression and enabling appropriate adjustments in response to ongoing assessments of treatment efficacy. Such a strategy should be a highly sophisticated process, not just the endpoint of a single stratification approach[16]. Accordingly, we reviewed two categories of biomarkers

(mainly from serum and feces) for IBD: Those used to identify disease progression risk and activity and those used to predict treatment responses.

Identifying disease progression risk and activity

C-reactive protein (CRP) is the most widely used serum biomarker for inflammation in IBD[17]. It reflects both clinical disease activity and endoscopic inflammation in IBD patients[18]. Additionally, the level of CRP is not influenced by treatments and thus is also suitable for monitoring treatment response[19]. However, it is not a specific biomarker, and its levels might be elevated in other diseases, including noninflammatory conditions. Additionally, up to 25% of Crohn's disease (CD) patients with endoscopically proven activity could not be identified by CRP[20]. Fecal calprotectin (FC) is another important noninvasive biomarker widely used in clinical practice. In the assessment of endoscopically defined disease activity in IBD, FC analysis exhibits higher sensitivity in the context of both ulcerative colitis (UC) and CD, especially in UC[21,22]. In particular, FC analysis could be used in the early prediction of relapse risk 6 and even 12 mo in advance[23]. A meta-analysis reported 78% sensitivity and 73% specificity when using FC at remission to predict IBD relapse, with cutoffs varying between 120 μg/g and 340 μg/g[24]. However, this biomarker also faces the problem of limited specificity; inflammation in the gut that is not associated with IBD, such as during infection, necrotizing enterocolitis and drug-induced enteropathy, could confound the results[25]. For patients with borderline FC levels, combining FC analysis with other metrics, such as clinical activity indices or CRP levels, could help the assessment[26]. The levels of serum calprotectin (SC), as an indirect marker of inflammatory activity in UC[27], can indicate the involvement of other extraintestinal organs. Another well-accepted fecal biomarker is fecal lactoferrin (FL), the levels of which could also reflect IBD activity and be used to predict disease relapse. Unlike the analysis of FC levels, the advantage of FL is its specificity[28], and combined analysis of these biomarkers might result in better assessment. In addition, some secondary biomarkers measured using simple laboratory tests, such as the CRP-albumin ratio,

neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR), can also be used to infer the activity of IBD[29,30].

In recent years, an increasing number of novel serum and fecal biomarkers with application potential have been discovered. The levels of leucine-rich glycoprotein, a glycoprotein that is also related to IBD activity, could be elevated in patients with normal CRP levels during the active period of UC[31]. Some serum antibodies resulting from autoimmunity and loss of immune tolerance to microbial antigens have been considered in the diagnosis and assessment of IBD[32]. For example, anti-*Saccharomyces cerevisiae* antibody (ASCA) and perinuclear anti-neutrophil cytoplasmic antibody (pANCA), which are antibodies of microbial antigens and autoantibodies, respectively[33], are two extensively studied antibodies with high specificity for IBD[34]. They could help identify potential CD patients five years before diagnosis when combined with the analysis of other protein markers[35]. In addition to enabling diagnosis, a higher ASCA titer was related to more aggressive fibrosis and stenosis and internal penetrating disease behaviors[36], while the pANCA titer changed with the activity of UC[37]. In addition, cytokines such as granulocyte colony-stimulating factor were associated with endoscopically active disease[38], while IL-6 and IL-2 Levels could also be used to predict the course of disease relapse 12 mo in advance in quiescent CD patients[39]. Circulating noncoding RNAs, including microRNAs (miRNAs) and long ncRNAs (lncRNAs), also play a role in IBD, and the analysis of miRNAs might help monitor disease activity and stricture phenotypes[32]. Other newly emerging biomarkers for disease progression risk and activity include cathelicidin[40], trefoil factor 3[41], and 25-hydroxyvitamin D3[42]. Several extracellular matrix (ECM) components and growth factors are important biomarkers indicating intestinal fibrosis and stenosis[32]. The analysis of fecal biomarkers, cytokines and other indicators of inflammation could also help with the identification of IBD activity[43]. Fecal myeloperoxidase, another biomarker related to neutrophil inflammation in addition to FC, was recently reported to accurately indicate endoscopic activity in IBD and predict the disease course during

follow-up[44]. However, all these novel biomarkers are mainly used in research and remain far from clinical use (Table 1).

Predicting treatment responses

The mainstream therapeutic drugs for IBD include aminosalicylates (ASAs), glucocorticoids (GCs) and immunosuppressive agents[45]. The treatment of IBD has greatly advanced since the recent introduction of biologics, including tumour necrosis factor-α (TNF-α) inhibitors (such as infliximab and adalimumab), integrin inhibitors (such as vedolizumab and etrolizumab) and IL-12/IL-23 inhibitors (such as ustekinumab). However, selecting among these therapies largely depends on the clinical characteristics, comorbidities, and patients' preferences or concerns, and this decision-making process lacks a uniform objective standard for indicating the path of treatment. Thus, effective biomarkers for predicting treatment responses are urgently needed.

For 5-ASA, a multicenter prospective cohort study in pediatric UC patients developed a predictive model with initial clinical activity and early treatment response to 5-ASA to predict long-term corticosteroid-free remission[46]. The baseline FC level and UC endoscopic index of severity could be used to predict the early outcome of GCs treatment[47].

Clinical responses to biologics are even more varied. However, the application of biologics is usually tried in a certain order by experienced physicians without effective biomarkers used to influence the selection of different kinds of biologics, which is of concern in research. Some laboratory test results are taken into consideration. For example, a clinical trial revealed that using CRP and FC levels in combination with clinical symptoms could result in better clinical and endoscopic outcomes than considering only clinical symptoms[48]. These downstream indicators of active inflammation could suggest a response to anti-inflammatory TNF-α inhibitors, but they are still not enough for accurate prediction of the likelihood of remission in a given

patient in a real clinical environment[49]. Thus, we need to explore more biomarkers that could reveal the molecular heterogeneity of patients treated with different biologics.

Existing biologics can be briefly classified into two groups according to underlying mechanisms: inhibitors of cytokines and inhibitors of lymphocyte migration. TNF-α is considered to be a downstream inflammatory pathway effector in multiple immune-related diseases[50]. It is rational to speculate that IBD patients with increased TNF-α levels might have a good response to anti-TNF-α agents. Detecting membrane-bound TNF (mTNF) by endoscopy with the aid of fluorescence labeling has been used to successfully predict the efficacy of anti-TNF-α treatment[51]. Another study also reached this goal by measuring the TNF production capacity of peripheral blood mononuclear cells (PBMCs)[52]. A lack of response to anti-TNF-α therapy might indicate the activation of other inflammatory pathways. Baseline levels of serum oncostatin M, a member of the IL-6 family that might mediate inflammation in another manner, have been reported to be elevated in anti-TNF-α nonresponders and could be used to predict the efficacy of this treatment[53,54]. In addition, low triggering receptor expressed on myeloid cells 1 (TREM1) expression in both whole peripheral blood samples and intestinal biopsy samples, which indicated a complete macrophage autophagy pathway, could be used to predict a good anti-TNF response in IBD patients[55]. Antibodies including anti-drug antibodies (ADA), pANCA and anti-OmpC (*Escherichia coli* outer membrane porin) were also found to be associated with the response to infliximab[56]. In the aspect of relapse after discontinuation of anti-TNF therapy, mucosal TNF gene expression and IL1RL1-transcripts might play a role[57].

The IL23/Th17 pathway is also a central cytokine pathway involved in IBD in addition to TNF-α. The levels of IL-22 and IL-17, the downstream factors involved in this pathway, are potential molecular predictors of the response to IL-23 blockers[58]. Another category of biologics for IBD is integrin inhibitors, which act by inhibiting gut-selective lymphocyte homing. The most widely used integrin inhibitor, vedolizumab, works by blocking the binding of the α4β7 integrin heterodimer on lymphocytes to MAdCAM1 on the gut[59]. Higher expression levels of α4β7 on T, B, and NK cells as well

as the presence of α4β7+ intestinal mucosa cells could be used to predict responses to vedolizumab[60,61]. However, the predictive role of serum α4β7, VCAM-1 and ICAM-1 remains controversial[62,63]. In addition, higher IL-6 and IL-8 Levels have been reported to be associated with the response to vedolizumab[64] (Table 2).

Sometimes, simply by assessing early responses to biologics, we can judge the potential future efficacy to some extent[65]. Therapeutic drug monitoring (TDM) is another tool for the assessment of biologic therapeutic outcomes based on the findings that drug concentrations correlate with biologic efficacy. However, due to the long time required for detection and the lack of an instructive reference range, there is still no consensus for the use of TDM[66,67].

FUTURE OF PRECISION MANAGEMENT IN IBD: MULTIOMICS

In addition to simple serum and fecal biomarkers, emerging high-throughput analytical technologies offer opportunities for the improved management of IBD. Omics strategies, often including genomics, transcriptomics, proteomics, metabolomics, epigenomics and microbiomics, have completely transformed the trajectory of medicine. These different omics approaches might also provide some insights into IBD from different perspectives.

Genomics

Genomics aims to characterize and quantify all the genetic information of an organism. Numerous variations in factors of genetic susceptibility involved in many complex diseases have been identified. Different genes have been reported to associate with IBD severity and activity. *NOD2/CARD15* is the most classic CD-related gene found in Western countries[68,69] and is also associated with stricturing behaviors and the need for operation[70,71]. However, it was not found to be related to CD development in East Asian cohorts[72]. Regarding UC, a GWAS developed a risk score based on 46 single nucleotide polymorphisms to identify medically refractory UC that needed colectomy[73]. Regarding therapeutic efficacy, HLA-DQA1*05 carriage was reported to

be associated with ADAs for TNF-α inhibitors in CD and suggested the need for combination therapy[74]. In addition, polymorphisms in *TLR2, TLR4, TLR9, TNFRSF1A, IFNG, IL6, IL1B, TNF-α* and apoptosis-associated genes (Fas ligand and caspase-6) were also potential genetic biomarkers for the anti-TNF treatment response[75-77]. HLA-DQA1-HLA-DRB1, nudix hydrolase 15 and thiopurine-S-methyltransferase variants were found to be associated with thiopurine-related adverse events[53]. However, the utility of genomics alone is limited due to the complexity of IBD pathogenesis.

Transcriptomics/proteomics/epigenomics: From genes to phenotypes

In exploring the pathogenesis of complex diseases such as IBD, the limitations of using a single genomics approach are becoming increasingly apparent. The same gene variation might lead to distinct phenotypes by epigenetic modification and transcriptional and translational regulation. Transcriptomics, proteomics and epigenomics could better reflect the gene expression profiles, which combine genetic and environmental factors and thus perform better than simple genomics.

In particular, numerous transcriptomic studies have provided insights into the prediction of IBD progression. Researchers found that the expression of ECM accumulation-associated genes in the ileum was associated with stricturing behaviors in pediatric CD patients. After combining age, race, disease location, and antimicrobial serology factors, they established a competing-risk model that reached a specificity of 71%[78]. However, ileum samples are difficult to access, which poses a barrier to the utility of this approach. Studies on blood samples are thus warranted. Transcriptional profiling of circulating CD8+ T cells successfully distinguished patients with a risk of aggressive disease mainly based on the expression of genes involved in T-cell responses[79]. Furthermore, this classification was also feasible for use in whole blood samples with transcriptional signatures based on 17 genes[80]. The transcriptional risk score, which represented the summation of risk alleles for CD from ileum or blood samples, could be used to identify patients who would progress to complicated disease[81]. Regarding treatment, UC patients could be clustered into different groups

with distinct transcriptomic profiles of the rectum and showed different responses to anti-TNF therapy[82].

Unlike transcriptomics, the use of proteomics in the context of IBD is still in its infancy. Some studies have sought to detect proteins involved in early inflammatory mechanisms of IBD, and some proteome analyses have been performed in studies with small sample sizes to investigate the differentiation of disease behavior as well as the prediction of response to biological treatment[83,84]. In the Proteomic Evaluation and Discovery in an IBD Cohort of Tri-service Subjects (PREDICTS) study, a series of protein biomarkers involved in the complement cascade, lysosomes, innate immune response, and glycosaminoglycan metabolism along with some antibodies were able to be used to predict potential CD patients 5 years in advance[35]. Another study revealed that MMP10, CXCL9, CXCL11, and MCP1 were upregulated in UC patients before disease onset[85]. However, there is still a long way to go before these approaches are applied clinically.

Epigenetic mechanisms mainly include DNA methylation, histone modifications, and noncoding RNAs. The complement of methylated DNA in the genome is called the methylome. Epigenetic alterations have been detected when IBD patients were compared with healthy individuals[86]. The number of epigenomic studies investigating IBD subgroup identification is still limited. The earliest finding observed in this area involved the assessment of cancer risk in the context of UC[87]. In future research, epigenomics studies might provide useful biomarkers for the early detection of cancer development in UC patients.

Microbiomics: Perspective of the environment

All of the above strategies provide omics analysis of the host. As mentioned previously, the gut microbiota, as an environmental factor, also plays an important role in the pathogenesis of IBD. Due to the convenience of fecal sample collection, microbiomics is promising for monitoring and managing IBD patients. The microbiota might also be able to be used to predict relapse risk. For example, a deficit in some bacterial groups or

species, such as *Faecalibacterium prausnitzii* and *Bacteroides,* could be a predictive factor for relapse of CD after ileal resection or infliximab cessation[88,89]. Another study revealed that *Ruminococcus* and *Veillonella* were associated with stricturing and penetrating complications, respectively[78]. A recent prospective study classified CD patients into different subgroups with different clinical relapse risk based on microbiota[90]. Additionally, microbial analysis revealed distinct microbiota compositions between patients with different responses to anti-TNF-α therapy[84,91] as well as anti-integrin therapy[92]. Furthermore, manipulation of the microbiota might be a direction for IBD treatment.

However, this method is easily influenced by environmental factors such as diet and confounded by the causal relationship between microbiota and IBD; thus, its reliability is questionable. Recent findings are still at a superficial stage of providing simple differences in microbial abundance, and there has been a lack of in-depth analysis of microbial networks and microbiota-host interactions, as well as solid and effective prediction models.

Metabolomics

Metabolomics generally includes serum and fecal metabolomics. As a combination of host metabolic factors and environmental gut microbiota factors, it is also a potential technique for use in future IBD research and clinical practice. Several studies have applied metabolic profiling for the diagnosis and classification of IBD[32]. A serum metabolomics study identified altered lipid and amino acid metabolism in parallel with CD activity[93]. Short-chain fatty acids (SCFAs) have been widely validated to be beneficial metabolites[94], among which butyrate is one of the most important. Studies have confirmed that fecal SCFA levels were reduced during active IBD[95]. Butyrate levels were associated with the efficacy of azathioprine, TNF-α inhibitors and integrin antibodies[92,96,97]. Other metabolites, such as bile acids and tryptophan, are also worth studying for future use[94].

APPLICATION OF ARTIFICIAL INTELLIGENCE FOR INTEGRATED OMICS

Due to the complexity of IBD pathogenesis, interpretation of a single set of omics data often fails to provide insight into complex biological phenomena; thus, the omics approaches discussed above must be considered as a whole. Integrating multiple omics strategies into a network would contribute to the elucidation of the pathway involved in pathogenesis and facilitate the identification of different subgroups and the optimization of therapy regimens in IBD. The analysis of different molecules, including at the genomic, transcriptomic, proteomic, microbiome, epigenetic and metabolomic levels, could be performed simultaneously, and the results could be further integrated into multiomics models[98]. By this approach, we could obtain more insight into disease pathogenesis, identify more promising predictive biomarkers and facilitate early diagnosis[99]. Some multiomics projects are ongoing and are investigating IBD heterogeneity to improve precision management[53].

These high-throughput data need to be modeled by AI algorithms with the aid of advanced computational techniques. Machine learning is a subset of AI where machines can learn from experience provided by the data without the need for programming. Machine learning includes supervised and unsupervised algorithms. Supervised algorithms are often used for classification or prediction using example data, while unsupervised algorithms are often used for clustering according to similarity[100]. These approaches could be well applied to address the need for patient clustering and predictions and the detection of novel biomarkers. Progress made in machine learning has benefited the integrated analysis of multiomics data; these strategies mainly include concatenation-, model- and transformation-based methods[101]. In addition, deep neural networks have been used in the integration of multiomics data for the prediction of drug efficacy in cancer therapy[102], which indicates progress may be made in the context of IBD.

However, due to the obscure nature of machine learning, the robustness of the models established is sometimes uncertain. Thus, testing in independent cohorts and even clinical trials are needed before this approach is employed in a clinical setting.

Additionally, products that are easy to implement in clinical settings need to be developed from research.

CONCLUSION

The pathogenesis of IBD remains uncertain, which challenges the clustering and precision management of patients. Genetic, environmental and immune factors are all involved in the complex process of IBD development. Thus, the future direction of IBD management may largely rely on the development of multiomics analysis. Numerous data processing workflows require the help of AI.

Figure 1 Flow gram of the precision management strategies of inflammatory bowel disease. IBD: Inflammatory bowel disease; PSC: Primary sclerosing cholangitis; VEO: Very early onset.

Table 1 Biomarkers of serum or feces identifying disease progression risk and activity

Sample	Biomarker	Outcome	Characteristic
Serum	CRP[17-20]	Monitor disease activity and mucosal healing	Widely used and low-cost; lack of specifi for intestinal inflammation; relatively sensitivity
	SCI[27,103]	Disease burden, prognosis, and relapse	More representative of systemic inflammati
	LRG[31]	Monitor disease activity and mucosal healing	More correlated to activity in UC than CRP
	Serum antibodies		
	ASCA[35,36]	More aggressive fibro stenosing and internal penetrating disease behaviors	CD specificity
	pANCA[35,37]	UC disease activity	UC specificity
	Cytokines		
	G-CSF, IL-1Ra, PDGF-BB[38]	Endoscopically active disease	-
	IL-6, IL-2[39]	Predict disease relapse in quiescent CD	-
	Noncoding RNAs[32]	Monitor disease activity and stricture phenotypes	-
	ECM components[32]	Intestinal fibrosis and stenosis	-
	Growth factors[32]	Intestinal fibrosis and stenosis	-

Sample	Biomarker	Clinical application	Characteristics
	Cathelicidin[40]	Mucosal disease activity in UC, risk of intestinal stricture in CD, and clinical prognosis in IBD	-
	Trefoil Factor 3[41]	Monitor disease activity	-
	Vitamin D[42]	Disease activity	-
	Secondary biomarkers (CRP-albumin ratio, NLR, PLR, LMR)[29,30]	IBD activity	Easy to obtain; fluctuates greatly
Feces	FC[21-26]	Monitor disease activity and mucosal healing; early prediction of relapse risk	Higher sensitivity than CRP; confounding non-IBD gut inflammation
	FL[28]	Monitor disease activity and predict disease relapse	Higher specificity than fecal calprotectin
	MPO[44]	Endoscopic activity in IBD and predict the disease course during follow-up	-

ASCA: Anti-*Saccharomyces cerevisiae* antibody; CD: Crohn's disease; CRP: C-reactive protein; ECM: Extracellular matrix; FC: Fecal calprotectin; FL: Fecal lactoferrin; G-CSF: Granulocyte colony-stimulating factor; IL-1Ra: Interleukin 1 receptor antagonist; IBD: Inflammatory bowel disease; LMR: Lymphocyte-monocyte ratio; LRG: Leucine-rich alpha-2 glycoprotein; MPO: Myeloperoxidase; NLR: Neutrophil-lymphocyte ratio; pANCA: Perinuclear anti-neutrophil cytoplasmic antibody; PDGF-BB: Platelet-derived growth factor BB; PLR: Platelet-lymphocyte ratio; SC: Serum calprotectin; UC: Ulcerative colitis.

Table 2 Biomarkers predicting treatment responses

Type of agent	Biomarker	Sample	Outcome
5-ASA	Initial clinical activity, early treatment response of 5-ASA[46]	-	Predict long-term corticosteroid-free remission
GCs	FC, UCEIS[47]	Feces	Predict the early outcome of GCs treatment
Biologics			
TNF-α inhibitors	mTNF[51]	Endoscopy	Predict anti-TNF-α efficacy
	TNF production capacity of PBMCs[52]	Blood	Predict anti-TNF-α efficacy
	OSM[53,54]	Serum	Upregulate in anti-TNF-α non-responders
	TREM1 expression[55]	Blood and intestinal biopsies	Predict anti-TNF-α efficacy
	Antibodies: ADA, pANCA, anti-OmpC[56]	Serum	Associate with the response to infliximab
	Mucosal TNF gene expression and IL1RL1- transcripts[57]	Intestinal biopsies	Predict 5 long-term remission after discontinuation of anti-TNF-α therapy
IL-23 inhibitors	IL-22, IL-17[58]	Serum	Predict anti-IL-23 efficacy
Integrin	α4β7 on T, B, and NK cells[60,61]	Blood and endoscopy	Predict responses to vedolizumab

| inhibitors | α4β7, VCAM-1, ICAM-1[62,63] | Serum | Remain controversial |
| | IL-6, IL-8[64] | Serum | Associate with the response to vedolizumab |

ADA: Anti-drug antibodies; ASA: Aminosalicylates; FC: Fecal calprotectin; GCs: Glucocorticoids; ICAM-1: Intercellular adhesion molecule-1; mTNF: Membrane-bound tumour necrosis factor; OmpC: *Escherichia coli* outer membrane porin; OSM: Oncostatin M; pANCA: Perinuclear anti-neutrophil cytoplasmic antibody; PBMC: Peripheral blood mononuclear cell; UCEIS: Ulcerative Colitis Endoscopic Index of Severity; VCAM-1: Vascular cell adhesion molecule-1; TREM1: Triggering receptor expressed on myeloid cells 1.

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