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Multi-Omics Biomarkers for Predicting Efficacy of Biologic and Small-Molecule Therapies in Adults With Inflammatory Bowel Disease: A Systematic Review

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ABSTRACT

The heterogeneity and suboptimal efficacy of biological treatments and small molecule drugs necessitate their precise selection based on biomarkers that predict therapeutic responses in inflammatory bowel disease. Recent studies have identified numerous novel biomarkers predictive of responses to biologics and small molecule modulators, utilizing a variety of omics approaches in inflammatory bowel disease. In this review, we systematically examine baseline omics biomarkers that predict responses to biological therapies and small molecule drugs, drawing on literature from PubMed. Our analysis spans multiple omics disciplines, including genomics, transcriptomics (both bulk RNA and single-cell RNA sequencing), proteomics, microbiomics, and metabolomics, with particular emphasis on the impact of models integrating multiple omics datasets. Additionally, to further the field of precision medicine, we evaluated specific biomarkers that may exhibit distinct effects on responses to multiple therapeutic interventions.

1 | Introduction

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory diseases characterized by intestinal injury and systemic inflammation [1]. Recently, there has been a notable increase in the development of novel biologics and small molecule drugs, thereby expanding therapeutic options for patients with IBD [2, 3]. Therefore, selecting the most appropriate biologics or small molecule drugs for managing IBD is crucial.

The inherent biological heterogeneity among individuals with IBD leads to the activation of different immune pathways and varied responses to specific biologics and small molecule drugs [4], resulting in suboptimal efficacy when agents are selected solely based on traditional factors such as patients' clinical characteristics, comorbidities, the cost and availability of therapy, and patient preferences [5–7]. Furthermore, the absence of direct comparative studies on the efficacy and safety of various biologics and small molecule drugs hinders the advancement of precision medicine in the management of IBD. Consequently, there is an urgent need for the development of novel biomarkers to stratify

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patients at a molecular level prior to the initiation of biologics and small molecule therapies, thereby optimizing the alignment of patients with the most appropriate therapeutic agents. This necessity is underscored by the significant costs, potential toxicities, and diminished response rates associated with second-line treatments following the failure of first-line therapies [8–10].

In this review, we examine novel baseline biomarkers encompassing a range of omics techniques with the potential to predict responses to biological therapies and small molecule drugs in patients with IBD. Ultimately, we specifically highlight biomarkers that have shown predictive potential for the efficacy of various drugs concurrently and may facilitate precise therapeutic selection in future clinical applications (Figure 1).

2 | Search Strategy

A comprehensive literature review was conducted using the PubMed database. The search terms were as follows (all fields): (Predict* OR Predicting OR Prediction OR Predictor* OR predictive) AND (Effect* OR Effectiveness OR Respond OR Response OR Responsiveness OR nonresponse OR non-response OR nonresponsiveness OR non-responsiveness) AND (Biologic* OR Biologic therapy OR Biological therapy OR Biologic treatment × OR anti-TNF* OR anti-tumor necrosis factor OR anti-tumor necrosis factor OR Infliximab OR Adalimumab OR Golimumab OR Certolizumab OR anti-integrin OR Vedolizumab OR anti-Interleukin-12/23 OR anti-IL-12/23 OR Ustekinumab OR anti-Interleukin-23 OR anti-IL-23 OR Risankizumab OR Brazikumab OR Mirikizumab OR Guselkumab OR anti-Interleukin-6 OR anti-IL-6 OR Olamkicept OR Oralizumab OR anti-TL1A OR small molecule drug* OR Janus Kinase Inhibitors OR JAK OR Tofacitinib OR Upadacitinib* OR Filgotinib OR Sphingosine1-Phosphate Modulators OR S1P) AND (Inflammatory Bowel Disease OR Crohn's disease OR Ulcerative colitis). References to the identified articles were also examined for additional studies meeting these criteria. A flowchart in accordance with the PRISMA 2020 flow diagram to elucidate the study selection process is presented in Figure S1.

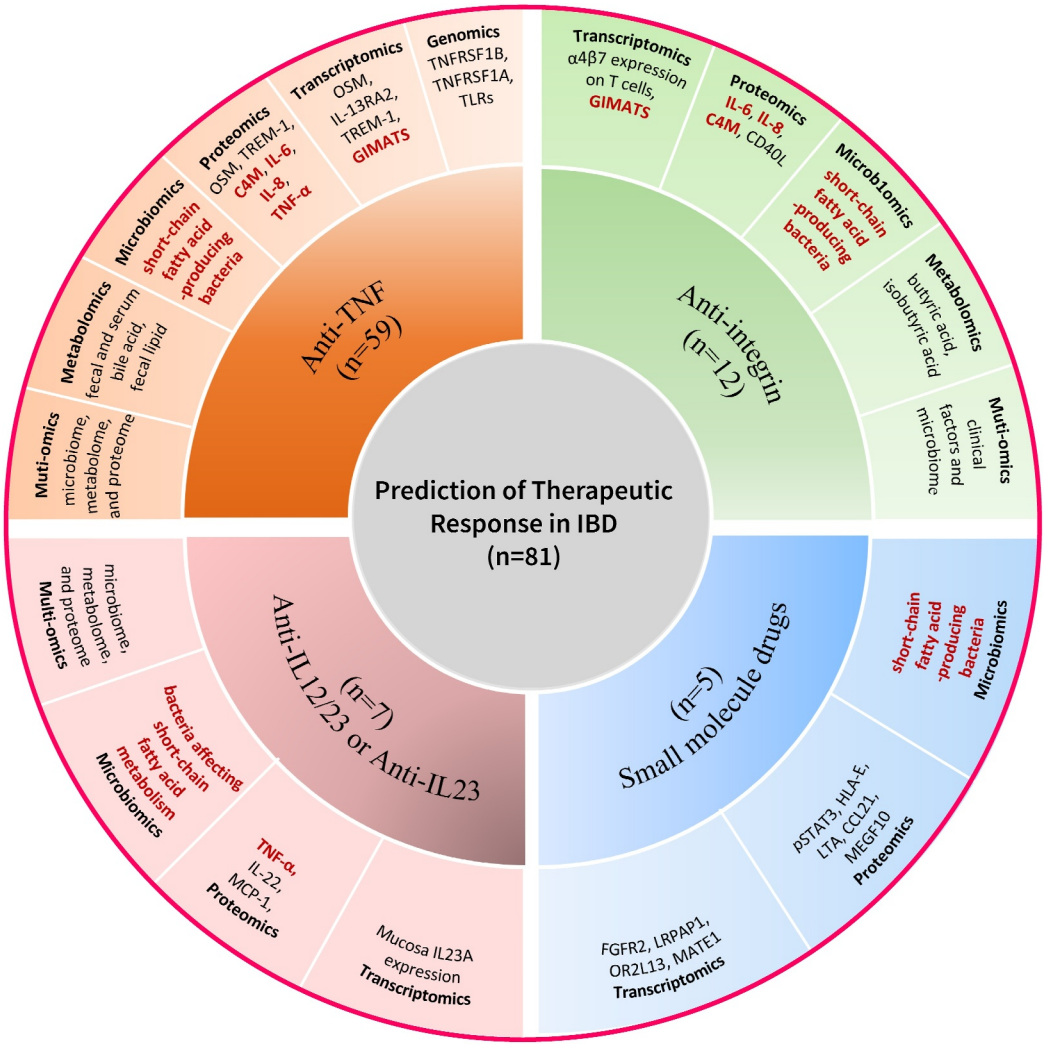

FIGURE 1 | Predicting the response to biologics and small molecule drugs using multi-omics baseline biomarkers, including genomics, transcriptomics, proteomics, microbiome, and metabolomics. The quantity of articles pertaining to each drug class, along with the representative biomarkers for each omic category within each drug class, is presented. The words highlighted in red denote biomarkers that have demonstrated predictive utility for the efficacy of various drugs concurrently.

3 | Anti-TNFα

Omics biomarkers predicting the response to anti-tumor necrosis factor alpha (anti-TNFα) involved genomics, transcriptomics, proteomics, microbiomics metabolomics, and integration of multiple omics biomarkers, of which relatively well-validated biomarkers are included in Table 1 and the supplemental biomarkers in Table S1. The detailed information of each study (such as study design, subjects included in these studies, drug investigated) was also summarized (Table S2).

3.1 | Genomics

Multiple genetic variants have been identified as predictive biomarkers for the response to anti-TNFα therapy in IBD. For example, TNFRSF1B (rs1061624) has been associated with a favorable response to anti-TNFα treatment in patients with CD [14, 15]. Similarly, TNFRSF1A (rs4149570) has been found to be associated with a beneficial response to anti-TNFα therapy in both CD and UC patients [16, 17]. What's more, Toll-like receptors (TLRs) have been extensively studied and demonstrate significant potential in predicting the efficacy of anti-TNFα agents in patients with IBD [15–18]. Specifically, TLR2 (rs1816702) has shown a positive correlation with response to anti-TNFα therapy in CD (hazard ratio [HR]: 0.128, 95% confidence interval [CI]: 0.02–0.99) [15]. Additionally, TLR2 (rs3804099), TLR4 (rs5030728), and TLR9 (rs187084) have exhibited positive correlations with response to anti-TNFα treatment in both CD and UC [15–18]. Moreover, genetic polymorphisms in IL23R have been identified as influencing the efficacy of anti-TNFα therapy in patients with both CD [19] and UC [20]. Despite the identification of genetic variants associated with susceptibility to IBD, research investigating the relationship between these genes and the efficacy of anti-TNFα therapy has generally yielded negative results. For instance, NOD2 was the first gene identified as being associated with CD susceptibility [55]. However, numerous studies have failed to demonstrate its predictive value regarding the efficacy of anti-TNFα therapy in CD [56–59].

3.2 | Transcriptomics

Arijs et al. [36] conducted a study on pre-treatment colonic mucosal expression profiles in two independent cohorts of UC patients. They identified a predictive model comprising five genes—TNFRSF11B, STC1, PTGS2, IL13Rα2, and IL11—that demonstrated an accuracy of 83% and 92% in predicting the efficacy of infliximab (IFX) in these cohorts, respectively. Notably, IL13Rα2 was validated in several independent cohorts of CD patients, where it was found to negatively predict the response to anti-TNFα therapy [26–28]. Subsequently, Arijs et al. [36] developed a model incorporating five key mucosal genes—TNFAIP6, S100A8, IL11, G0S2, and S100A9—that achieved 100% accuracy in distinguishing between responders and non-responders to IFX among 19 patients with Crohn's colitis [34]. Within this gene set, the expression levels of S100A8 (area under the curve [AUC]: 0.759, 95% CI: 0.527–0.991) and S100A9 (AUC: 0.857, 95% CI: 0.645–1.000) demonstrated significant predictive value for IFX response in a separate cohort of patients with UC [30]. Oncostatin M (OSM) has also been well-established in both CD and UC [23, 24]. For instance, West et al. [24] demonstrated that mucosal healing following IFX treatment was achieved in 69%–85% of IBD patients exhibiting low OSM module expression, compared with only 10%–15% of patients with high OSM module expression. What's more, mucosal and blood triggering receptor expressed on myeloid cells-1 (TREM1) expression was identified as a potential biomarker for predicting the response to anti-TNFα in both CD and UC, although the data remains inconsistent [25, 29–33].

Single-cell RNA sequencing (scRNA-seq) technologies offer enhanced insights and more precise analyses. Jerome et al. [40] identified a distinctive cellular module termed GIMATS, comprising IgG plasma cells, inflammatory mononuclear phagocytes, activated T cells, and stromal cells, which serves as a predictive marker for treatment failure with anti-TNFα therapy in patients with IBD. Subsequent investigation of this cellular module in an additional IBD cohort demonstrated its potential in guiding the selection of the most appropriate therapeutic intervention between IFX/ADA and VDZ [39].

3.3 | Proteomics

Most studies exploring protein biomarkers adopt a serum-based methodology. In parallel with OSM expression in intestinal tissue, elevated serum OSM levels also exhibited a negative predictive value for mucosal healing in patients with CD and UC treated with IFX, with an AUC ranging from 0.88 to 0.938 [41–43]. Similarly, serum TREM-1 was identified as a negative predictor of endoscopic response to anti-TNFα therapy in IBD patients, demonstrating an accuracy of 94% [60]. However, it showed poor predictive performance in a separate IBD cohort [32]. Algaba et al. [61] conducted a study on patients with IBD and found that lower serum levels of vascular endothelial growth factor (VEGF) were associated with a better clinical response to anti-TNFα therapy. However, a subsequent investigation focusing on patients with CD identified elevated serum VEGF levels as a positive biomarker for predicting clinical response to anti-TNFα therapy [62].

3.4 | Microbiomics and Metabolomics

The microbiome, recognized as a critical element in the pathogenesis of IBD, has shown potential in forecasting the efficacy of anti-TNFα therapy [46–48, 50, 51]. Notably, reduced levels of short-chain fatty acid-producing bacteria, particularly *Clostridia*, *Coprococcus*, and *Lachnospira*, in conjunction with elevated levels of certain common intestinal bacteria such as *Klebsiella*, *Eubacteriaceae*, *Bifidobacterium animalis*, and *Candida*, have been identified as predictors of diminished response to anti-TNFα treatment in IBD patients [46, 50]. In a supplementary study involving patients with IBD, clinical responders to anti-TNFα therapy exhibited significantly elevated levels of *Firmicutes*, *Clostridia*, and *Ruminococcaceae* in their stool samples compared to non-responders [47]. Moreover, Aden et al. [48] identified that a reduction in metabolic interactions among gut microbes at baseline was associated with

TABLE 1 | Baseline predictors of response to anti-TNF in IBD.

Predictors	Disease type	Predictive value	Predicted outcome
Genomics			
TNFα −308 GG genotype	CD&UC	OR: 2.31, 95% CI: 1.36–3.91 [11] OR: 2.88, 95%CI: 1.01–8.22 [12]	Favorable response
TNFα −857 C/C genotype	CD&UC	OR: 3.66, 95% CI: 1.35–9.92 [11] OR: 0.33, 95% CI: 0.12–0.95 [13]	Favorable response
TNFRSF1B (rs1061624) AA or GA genotype	CD	OR: 1.78, 95% CI: 1.09–2.90 [14] HR: 0.04, 95%CI: 0.18–0.92 [15]	Negative response
TNFRSF1A (rs4149570) TT genotype	CD&UC	ORa: 2.07, 95% CI: 1.03–4.15 [16] OR: 1.92, 95% CI: 1.02–3.60 [17]	Favorable response
TLR2 (rs3804099) TT genotype	CD&UC	ORa: 1.80, 95% CI: 1.15–2.81 [16] HR: 0.039, 95%CI: 0.18–0.88 [15] OR: 0.3285, 95% CI: 0.132–0.811 [18]	Contradictory
TLR2 (rs1816702) CC/CT genotype	CD	HR: 0.128, 95%CI: 0.02–0.99 [15]	Favorable response
TLR4 (rs5030728) GA/AA genotype	CD&UC	ORun: 1.45, 95% CI: 1.06–2.00 [16] OR: 2.23, 95% CI: 1.24–4.01 [17]	Favorable response
TLR9 (rs187084) TC genotype	CD&UC	ORa: 1.99, 95% CI: 1.04–3.82 [16]	Favorable response
IL23R variants	CD&UC	HRa: 0.41; 95% CI: 0.22–0.75 [19, 20]	Favorable response
A model of CCDC88B (rs61886887), C1orf106 (rs61740234), OSMR (rs357291), TRIM21 (rs2269330) and FCGR3A (rs111504845)	CD	AUC = 0.794, 95% CI: 0.682–0.905 [21]	—
A model consisting of 15 SNPs and a model consisting of 16 SNPs	CD	AUC = 0.934 and 0.83 respectively [22]	—
Transcriptomics			
OSM	CD&UC	AUC = 0.737, 95% CI: 0.537–0.937 [23, 24]	Negative response
OSMR	CD&UC	AUC = 0.763, 95% CI: 0.556–0.969 [25]	Negative response
IL13RA2	CD	AUC = 0.90 for IFX and 0.94 for ADA [26] AUC = 0.810, 95% CI: 0.740–0.880 [27] ORa: 0.06, 95% CI: 0.01–0.92 [28]	Negative response
TLR2	CD&UC	AUC = 0.829, 95%CI: 0.680–0.979 [29] AUC: 0.741, 95%CI: 0.520–0.962 [30]	Negative response
TREM1	CD&UC	AUC = 0.844, 95%CI: 0.716–0.873 [29] AUC = 0.94 [25] AUC = 0.80, 95%: 0.60–1.00 [31] AUC = 0.78, 95% CI: 0.65–0.90 [32] AUC: 0.759, 95%CI: 0.540–0.977 [30–33]	Contradictory
S100A8	UC	AUC: 0.759, 95%CI: 0.527–0.991 [30]	Negative response
S100A9	UC	AUC: 0.857, 95%CI: 0.645–1.000 [30]	Negative response
A model of TNFAIP6, IL11, G0S2, S100A8, S100A9	CD	Accuracy = 1 [34]	—

(Continues)

TABLE 1 | (Continued)

Predictors	Disease type	Predictive value	Predicted outcome
A model of CDX2, CHP2, HSD11B2, RANK, NOX4, and VDR	UC	AUC = 0.850 ± 0.103 [35]	—
A model of TNFRSF11B, STC1, PTGS2, IL13Ralpha2, IL11	UC	Accuracy is 83.3% and 90.9% in two cohorts respectively [36]	—
A model of BTN3A2, CD300E, ENDOD1, FMN1, KAT2B, ODC1, PBX1and UBE2H	CD	AUC = 0.97 [37]	—
A mode of DPY19L3, GSTT1, and NUCB1	CD	AUC = 0.928 in training set and 0.943 in testing set [38]	—
GIMATS module	CD&UC	AUC = 0.720 for IFX/ADA and 0.728 for VDZ [39, 40]	Negative response
Proteomics			
Serum OSM	CD&UC	AUC = 0.91 [41] AUC = 0.91 [42] CD: AUC = 0.880; UC: AUC = 0.938 [43]	Negative response
A model of serum TGF-β1 and CD14	CD&UC	AUC = 0.936 [44]	—
A model of TNF-α, IL-13, OSM, and IL-7	CD	—[45]	—
Microbiomics			
Short-chain fatty acid-producing bacteria (*Anaerostipes*, *Coprococcus*, *Lachnospira*, etc.)	CD&UC	—[46]	Favorable response
Firmicutes, Clostridia, Ruminococcaceae, Prevotella and Acidovorax caeni.	CD&UC	—[47]	Favorable response
Metabolic interactions between gut microbes	CD&UC	—[48]	Favorable response
A random forest model of microbes (multiple Clostridiales OTUs are the most contributive)	CD	Accuracy = 86.5% [49]	—
A model of short-chain fatty acid producers e. t. *Clostridia* and pro-inflammatory bacteria and fungi e. t. *Candida*	CD&UC	AUC = 0.933 for CD and 0.818 for UC [50]	—
A model of 4 microbial markers	CD&UC	Sensitivity = 93.3%; Specificity = 100% [51]	—
Metabolomics			
5 bile acid markers in serum	CD	AUC = 0.74 ± 0.15 [52]	—
3 bile acid markers in feces		AUC = 0.81 ± 0.17 [52]	
5 bile acid markers in urine		AUC = 0.70 ± 0.17 [52]	
urinary cysteine	CD	AUC = 0.70 ± 0.14 [52]	Favorable response
Histidine in serum and feces	CD	AUC = 0.48 ± 0.18 [52] AUC = 0.63 ± 0.28 [52]	Favorable response
Multi-omics			
A model integrating clinical, metagenomic, metabolomic and proteomic data	CD&UC	AUC = 0.96, 95% CI: 0.88–1.00 [53]	—
A model integrating DNA methylation and gene expression	CD	AUC = 1.00 [54]	—

Abbreviations: 95% OR, odds ratio; ADA, adalimumab; AUC, area Under Curve; C4M, matrix metalloproteinase-derived fragments of type IV collagen; CD, Crohn's disease; CI, 95% confidence interval; HR, hazard ratio; HRa, adjusted HR; IFX, infliximab; ORa, adjusted OR; ORun, unadjusted OR; RR, relative risk; OTUs, operational Taxonomic Units; UC, Ulcerative colitis; VDZ, vedolizumab.

unfavorable clinical outcomes in IBD patients undergoing anti-TNF treatment. Additionally, a pilot study developed an algorithm incorporating four bacterial markers, which effectively distinguished between responders and non-responders to anti-TNFα therapy, achieving a sensitivity of 93.3% and a specificity of 100% [51].

The interplay between the gut microbiota and the host is frequently mediated by metabolites, which have also demonstrated potential in predicting responses to anti-TNFα therapy [52]. In a prospective cohort study involving 76 patients with CD [52], histidine and cysteine levels in serum and urine were identified as positive biomarkers for clinical response to anti-TNFα treatment. Conversely, phosphocholines, ceramides, sphingomyelins, triglycerides, and primary bile acids in serum and feces were identified as negative biomarkers for clinical response to anti-TNFα therapy.

3.5 | Integration of Multi-Omics Data

Lee et al. [53] identified a correlation among microbial diversity, species capable of 7α/β-dehydroxylation of primary to secondary bile acids, serum metabolites such as secondary bile acids, and serum proteins in a multi-omics study involving IBD patients. The integrative model, which incorporates clinical, metagenomic, metabolomic, and proteomic biomarkers identified in this study, demonstrated superior performance compared to a model based solely on baseline clinical features for predicting clinical response to anti-cytokine therapy (anti-TNFα and anti-IL12/23), achieving an AUC of 0.963 versus 0.624. Additionally, Mishra et al. [54] conducted both single-omics analyses—utilizing peripheral blood gene expression data and DNA methylation features—and integrated analyses in patients with CD. Their findings indicated that the integrated model demonstrated superior performance in predicting the response to anti-TNFα therapy at week 14 and achieved an AUC of 1.

4 | Anti-Integrin

Varieties of omics biomarkers predicting the response to anti-integrin therapy were also investigated and included in the Table 2. In comparison to predictive biomarkers for anti-TNFα, those for anti-integrin encompass a narrower range of omics techniques, notably lacking genetic biomarkers. Furthermore, most of these biomarkers have not been well-validated in independent cohorts.

4.1 | Transcriptomics

Verstockt et al. [66] identified 4 genes (PIWIL1, MAATS1, RGS13, and DCHS2) for predicting the efficacy of vedolizumab (VDZ), which could distinguish patients with IBD who achieved remission from those who did not, with high accuracy in both training (80%) and validation (100%) datasets. In alignment with prior research [73, 74], the expression levels of peripheral blood T cell α4β7 integrin and its adhesion capability to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) were confirmed to be positively correlated with clinical response to VDZ in a prospective multi-center cohort study involving patients with UC [63].

In a recent study involving a cohort of 13 patients with UC, researchers investigated the cellular mechanisms underlying the efficacy of VDZ by examining the interactions between T helper 17 (Th17) cells and other immune cells [65]. The findings indicated that individuals who responded to VDZ treatment exhibited reduced proportions of Th17 cells at baseline. Additionally, Th17 cells from non-responders demonstrated increased interactions with classical monocytes.

4.2 | Proteomics

Baseline serum IL-8 was identified as positively correlated with the response to VDZ in both CD and UC patients [68]. Moreover, serum IL-6 has been examined in multiple studies involving IBD patients, but its predictive value has shown inconsistency [68, 69, 75]. In a study conducted by Christoffer et al. [69], involving patients with both CD and UC, it was found that elevated levels of soluble CD40 ligand (sCD40L) predicted treatment failure of VDZ in CD patients with a sensitivity of 100% (95% CI: 59%–100%). Conversely, higher levels of osteocalcin predicted a positive response to VDZ in UC patients with a sensitivity of 85% (95% CI: 55%–98%). Recently, serological biomarkers indicative of intestinal collagen turnover have been examined in patients with CD [70]. Notably, C4M emerged as a negative predictor of the durable efficacy of VDZ, demonstrating an AUC of 0.77 (95% CI: 0.60–0.93). However, further research is warranted to substantiate these findings.

4.3 | Microbiomics and Metabolomics

Ananthakrishnan et al. [71] identified several baseline characteristics predictive of clinical remission with VDZ at week 14. For CD, their model incorporated α-diversity, β-diversity, the abundance of butyrate producers, and 13 microbial pathways, including those involved in branched-chain amino acid biosynthesis, achieving an AUC of 0.881. For UC, the model included two enriched pathways and three depleted pathways with AUC of 0.853. Correspondingly, a study on the metabonomic profiles of UC patients demonstrated that higher baseline levels of butyric acid and isobutyric acid in feces were predictive of a favorable response to anti-integrin therapy [72].

4.4 | Integration of Multi-Omics Data

In a cohort of 29 patients with moderate to severe UC, Liu et al. [72] found that Verrucomicrobiota abundance (AUC = 0.897; 95% CI: 0.764–1.000), butyric acid (AUC = 0.750; 95% CI: 0.567–0.933) and isobutyric acid (AUC = 0.725; 95% CI: 0.533–0.918) in feces could predict treatment response to VDZ at week 14. Subsequently, the integration of these microbiota and metabolic markers yielded an AUC of 0.961, surpassing the AUC obtained when utilizing microbiota or metabolites independently.

5 | Anti-IL12/23p40 or Anti-IL23p19

Although much less than anti-TNFα and anti-integrin agents, attempts have been made to explore omics biomarkers that have the potential to predict the efficacy of anti-IL12/23p40 or anti-

TABLE 2 | Baseline predictors of response to anti-integrin in IBD patients.

Predictors	Disease type	Predictive value	Predicted outcome
Transcriptomics			
Abundance of α4β7-expressing CD3+ T cell	CD&UC	AUC = 0.706, 95% CI: 0.593–0.819 [63]	Favorable response
FFAR2-NRF1	UC	AUC = 0.81 [64]	Favorable response
CSF3R-RELB	UC	AUC = 0.80 [64]	—
ITGB4-ETS1	UC	AUC = 0.80 [64]	—
GIMATS module	CD&UC	AUC = 0.720 for IFX/ADA and 0.728 for VDZ [39]	Favorable response
Proportions of TH17 cells, and colon TH17 cells' interactions with classical monocytes	UC	—[65]	Negative response
A model of PIWIL1, MAATS1, RGS13, and DCHS2	CD&UC	Accuracy of 80% in training cohort and 76.9%–100% in 3 validation cohorts [66]	—
A model of CXCL9, PIWIL1, OSM, SELE, CCL5, CXCL5, CXCL6, RGS13, LTB, CEBPB, IL23A, DCHS2, CXCL10	UC	Accuracy of 97.5% in discovery cohort and 95% in validation cohort [67]	—
Proteomics			
Serum IL-6	CD&UC	AUC = 0.77, 95% CI: 0.57–0.98 [69]—[68]	Contradictory
Serum IL-8	CD&UC	—[68]	Favorable response
soluble CD40 ligand	CD	AUC = 1.00, 95% CI: 1.00–1.00 [69]	Negative response
serum osteocalcin	UC	AUC = 0.92, 95% CI: 0.79–1.06 [69]	Favorable response
serum CPa9-HNE	CD	AUC = 0.81, 95% CI: 0.66–0.96 [70]	Negative response
serum C1M	CD	AUC = 0.85, 95% CI: 0.75–0.98 [70]	Negative response
serum C3M	CD	AUC = 0.79, 95% CI: 0.62–0.95 [70]	Negative response
serum C4M	CD	AUC = 0.77, 95% CI: 0.60–0.93 [70]	Negative response
serum C6Ma3	CD	AUC = 0.75, 95% CI: 0.58–0.92 [70]	Negative response
serum PRO-C4/C4G	CD	AUC = 0.72, 95% CI: 0.54–0.90 [70]	Negative response
Microbiomics			
A model of α-diversity, β-diversity, 13 microbial pathways and abundance of butyrate producers	CD	AUC = 0.881 [71]	—
A model of 2 enriched pathways and 3 depleted pathways	UC	AUC = 0.853 [71]	—
Multi-omics			
A model incorporating abundance of *Verrucomicrobiota*, levels of butyric acid and isobutyric acid in feces	UC	AUC = 0.961; 95% CI: 0.882–1.000 [72]	—

Abbreviations: 95% CI, 95% confidence interval; AUC, area Under Curve; C1M, matrix metalloproteinase-derived fragments of type I collagen; C3M, matrix metalloproteinase-derived fragments; CD, Crohn's disease; CPa9-HNE, human neutrophil elastase-derived fragments of calprotectin; DEGs, differentially expressed genes; PBMC, peripheral blood mononuclear cell; UC, Ulcerative colitis.

TABLE 3 | Baseline predictors of response to anti-IL12/23p40, anti-IL23p19 and small molecule drugs in IBD patients.

Predictors	Disease type	Predictive value	Predicted outcome
anti-IL12/23p40 or anti-IL23p19			
Transcriptomics			
IL23A	CD&UC	AUC = 0.90 [76]	Favorable response
A model of HSD3B1, MUC4, CF1, and CCL11	CD	AUC = 0.746 in the training set and 0.734 in the testing set [77]	—
Proteomics			
Serum IL22	CD	—[78]	Favorable response
Serum TNF-α	CD	AUC = 0.819 [79]	Favorable response
Serum MCP-1	CD	HR: 1.038, 95% CI: 1.015–1.062 [80]	Negative response
Microbiomics			
A random forest model trained on fecal microbial data (*Faecalibacterium* and *Escherichia* are the most predictive OTUs)	CD	AUC = 0.838 [81]	—
Multi-omics			
A model integrating clinical, metagenomic, metabolomic and proteomic data	CD&UC	AUC = 0.96, 95% CI: 0.88–1.00 [53]	—
Small molecule drugs			
Transcriptomics			
MATE1	UC	—[82]	Favorable response
A model utilizing a combination of 53 predictor CpGs	UC	AUC = 0.74 [83]	—
A cluster of 65 genes in the mucosa	UC	—[84]	—
Proteomics			
pSTAT3 in non-epithelial colonic segments	CD	OR = 0.07, 95% CI = 0–0.75 [85]	Favorable response
A model of four baseline serum proteins—HLA-E, LTA, CCL21, and MEGF10	UC	AUC = 0.83–0.88 [86]	—
Microbiomics			
Butyricimonas, Peptostreptococcus, Alistipes, Methanobrevibacter, and Parabacteroides	UC	—[86]	Favorable response

Abbreviations: 95% CI, 95% confidence interval; AUC, area Under Curve; CD, Crohn's disease; HR, hazard ratio; OR, odds ratio; OTUs, operational Taxonomic Units; UC, Ulcerative colitis.

IL23p19. These promising biomarkers are exhibited in the Table 3.

5.1 | Transcriptomics

He et al. [77] developed a predictive model consisting of four genes (HSD3B1, MUC4, CF1, and CCL11) for ustekinumab (UST) efficacy prediction in patients with CD with AUC of 0.746 and 0.734 in the training set and testing set, respectively. In a prospective study involving IBD patients, lower baseline IL23A expression in mucosal biopsies was found to predict non-response to UST with an AUC of 0.90 [76].

5.2 | Proteomics

Murate et al. [79] identified a positive correlation of serum TNF-α with clinical response to UST in CD patients (AUC = 0.819). As a downstream effector of IL-23, serum IL-22 has been shown to be positively correlated with the persistence of anti-IL-23 therapy in patients with CD [78]. Moreover, a recent study

has identified serum monocyte chemoattractant protein-1 (MCP-1) as a biomarker that negatively predicts the long-term efficacy of UST in CD patients, with an AUC of 0.694 at one year and 0.670 at two years [80].

5.3 | Microbiomics

Doherty et al. [81] developed a random forest model utilizing baseline microbiota data to predict clinical remission after 6 weeks of UST treatment in patients with CD, achieving an AUC of 0.838. Specifically, two operational taxonomic units (OTUs) affiliated with *Faecalibacterium* and *Bacteroides* showed the most significant predictive value and higher baseline abundance in subjects in remission compared with those with active CD.

5.4 | Integration of Multi-Omics Data

As previously discussed in the section on Anti-TNFα, Lee et al. [53] demonstrated that a model incorporating clinical, metagenomic, metabolomic, and proteomic biomarkers significantly outperformed a model based solely on baseline clinical features in predicting the clinical response to anti-cytokine therapy (anti-TNFα and anti-IL12/23) in patients with IBD [53]. The integrated model achieved an AUC of 0.963, compared to an AUC of 0.624 for the clinical model.

6 | Small Molecule Drugs and Other Novel Biologics

We additionally conducted a review of studies examining predictive biomarkers for responses to small molecule drugs, including Janus Kinase (JAK) inhibitors and Sphingosine-1-Phosphate (S1P) modulators, as well as novel biologics such as anti-IL6 and anti-TL1A (Tumor Necrosis Factor-like Cytokine 1A). While several studies have investigated baseline omics biomarkers predictive of responses to small molecule drugs (as summarized in Table 3), there is currently a lack of research on such biomarkers for these novel biologics.

6.1 | Transcriptomics

Joustra et al. [83] conducted a study involving 31 young Caucasian patients with moderate-to-severe UC treated with Tofacitinib, an oral small molecule JAK inhibitor. The researchers developed a predictive model that could distinguish responders from non-responders at Week 8 with considerable accuracy (AUC = 0.74), utilizing a combination of 53 predictor CpGs (cytosine-phosphate-guanine sites). Among the top 25 markers, 15 CpG loci were annotated to 14 unique genes, of which MAGI3, ERICH1, *HLA*-DQB1, PALD1, BTNL9, and LMLN2 exhibited hyper-methylation, whereas RPTOR, CLCA1, HLA-DRB1, HLA-DRB5, OR2L13, RP11-526L2.5, SPATC1L, and MRPL28 exhibited hypo-methylation in responders compared to non-responders. Furthermore, gene expression analysis of genes annotated to the 53 predictor CpGs showed a significantly lower expression of FGFR2 and LRPAP1, and a significantly higher expression of OR2L13 at baseline, in responders compared with non-responders. In a study involving 16 patients with UC treated with Tofacitinib [84], an unbiased network analysis identified a cluster of 65 genes in the mucosa that was significantly correlated with endoscopic response at weeks 8–14 ($p = 0.006$). The hub gene within this cluster was the most differentially expressed gene ($p = 1.5E{-}9$, fold change = 2.3), demonstrating a predictive accuracy of 100%. Additionally, the expression levels of OSM ($p = 0.62$), TREM1 ($p = 0.70$), IL13RA2 ($p = 1.0$), and a 4-gene signature comprising MAATS1, PIWIL1, RGS13, and DCHS2 were examined, but none showed a correlation with the response. Jang et al. [82] investigated the levels of MATE1, OCTN1/2, and JAK1 using western blot analysis in organoids derived from patients with UC prior to the initiation of tofacitinib treatment. Their findings indicated that the protein level of MATE1 was significantly lower in organoids from non-responders, whereas no correlation was observed for the other two markers. Subsequent transcriptome analysis of MATE1 in organoids corroborated these results, which were further validated in colonic tissue samples from the same UC patients from whom the organoids were cultured. Additionally, the study explored microbial factors associated with tofacitinib responsiveness but did not yield any significant findings.

6.2 | Proteomics

By employing immunohistochemistry to quantify phosphorylated signal transducer and activator of transcription 1 (pSTAT1) and pSTAT3 in both epithelial and non-epithelial tissues, it was determined that baseline levels of pSTAT3 in non-epithelial colonic segments are predictive of endoscopic response to filgotinib, an oral JAK1 inhibitor, at Week 10 in patients with CD (odds ratio (OR) = 0.07, 95% CI = 0, 0.75, $P = 0.044$) [85]. A post hoc analysis of the Phase 2b VIBRATO study identified four baseline serum proteins—HLA-E, LTA, CCL21 and MEGF10—in patients with UC that significantly differentiated responders from non-responders to ritlecitinib, an oral JAK3 inhibitor [86]. This differentiation was evaluated based on clinical and endoscopic outcomes, with a false discovery rate (FDR) of ≤ 0.15. A predictive model incorporating these four proteins demonstrated excellent performance, with an AUC of 0.83 (95% CI: 0.70–0.97) for clinical response and an AUC of 0.88 (95% CI: 0.77–0.99) for endoscopic response.

6.3 | Microbiomics

Hassan-Zahraee et al. [86] conducted a metagenomic analysis of stool samples from patients with UC and identified five bacterial taxa—*Butyricimonas, Peptostreptococcus, Alistipes, Methanobrevibacter, and Parabacteroides*—that were associated with endoscopic response to ritlecitinib. Additionally, three of these taxa—*Butyricimonas*, *Methanobrevibacter*, and *Parabacteroides*—were found to be correlated with clinical response.

7 | Specific Biomarkers Potentially Aid in the Precise Selection of Biological Treatments for IBD

Given that each biological treatment has a unique mechanism of action, it is reasonable to believe that there exist biomarkers indicating patients' preference for a particular biologic or small molecule drugs, thereby contributing to precise selection of them. Current investigations have identified several biomarkers of this potential (Figure 2). Y. Chen et al. [75] and Billiet et al. [87] found IL-6 and IL-8 concentrations in serum were negatively correlated with the response to IFX in CD patients. Nevertheless, the serum levels of IL-6 and IL-8 demonstrated positive correlations with the response to VDZ in CD patients [68]. Alexdottir et al. [70, 88] measured serological biomarkers of extracellular matrix turnover in two cohorts of CD patients using IFX and VDZ, respectively, finding that C4M was elevated at baseline in responders of IFX but non-responders of VDZ. Several researches demonstrated a negative correlation between the response to IFX and serum concentration of TNF-α [45, 89], which was higher at baseline in CD patients reaching clinical response on UST [79]. By scRNA-seq, a unique cellular module called GIMATS was identified, and helped to categorize IBD patients into 3 groups: M type (GIMATS-low, metabolism), with a preference for IFX/ADA; I type (GIMATS-high, immune), with a preference for VDZ; and N type (GIMATS-medium, normal), with no specific preference for either treatment [39, 40]. Another study demonstrated that IBD patients in Metacommunity DMM Group 1, predominantly represented by microbial species of the Firmicutes phyla, exhibited a preferential response to anti-cytokine therapy (anti-TNF or -IL12/23) over anti-integrin [53].

These biomarkers, which can predict the efficacy of several different biological agents, require well-designed cohorts to be validated. At the same time, more novel biomarkers with such potential need to be investigated to advance precision medicine in IBD.

8 | Challenges and Future Directions

Currently, an increasing number of researches investigate novel biomarkers using advanced omics techniques for predicting responses to biological treatments and small molecule drugs in IBD patients. In addition to the conventional analysis, many novel analytical techniques have gained considerable attention, including scRNA-seq, machine learning, systems biology and so on [39, 40, 53, 54, 65, 72, 90]. These emerging biomarkers and technologies enhance the prediction of responses to various biologics and small molecule modulators in IBD. Promisingly, several biomarkers show potential to aid precise selection of these therapeutic options, including GIMATS module, C4M and so on.

FIGURE 2 | Biomarkers that have shown predictive utility for the efficacy of various drugs concurrently and may facilitate the precise selection of therapeutic agents in future clinical applications. The correlation between these biomarkers and the efficacy of each drug is represented through distinct color coding. CD, Crohn's disease; GIMATS module, a cellular module consisting of IgG plasma cells, inflammatory mononuclear phagocytes, activated T cells, and stromal cells; IBD, inflammatory bowel disease.

However, several challenges still persist limiting the identification and utilization of reliable biomarkers. (1) The majority of current studies primarily focus on anti-TNF-α agents, while investigations into novel biomarkers for emerging biologics and small molecule drugs remain limited. This disparity hampers the accurate selection and optimization of these therapeutic options. (2) Small sample size is a common limitation in many studies, resulting in inadequate statistical power. (3) The heterogeneity in disease subtypes, study endpoints, and methodologies used across various studies hinders the comparison and integration of results. (4) Integrating multiple omics necessitates precise selection based on the simultaneous processing of extensive data, posing significant challenges in bioinformatics analysis. (5) In the clinical translation of biomarkers, there remains a significant deficiency in head-to-head clinical trials comparing various biologics and small molecule drugs, as well as in large-scale, multicenter cohort studies conducted in real-world settings to validate potential biomarkers. (6) Given the disparities in medical resources across various regions, the implementation of biomarker-based precision medicine has the potential to further exacerbate these imbalances.

Therefore, a collective effort is required. Firstly, it is recommended to establish multi-center cohorts to enhance statistical power and mitigate population differences across medical centers. Additionally, meticulous study design, such as the incorporation of biomarkers into early-stage clinical trial protocols, is also essential for the identification of reliable predictive biomarkers. When investigating biomarkers, it is also imperative to ensure a balanced approach between various agents by addressing the deficiencies in biomarkers for both emerging biologics and small molecule drugs. Promisingly, incorporating advanced technologies such as spatial transcriptomics, single-cell sequencing, systems biology, and artificial intelligence holds substantial potential for the in-depth exploration of predictive biomarkers [91, 92]. Given the significance of clinically translating identified biomarkers, it is essential to validate the efficacy of these promising biomarkers through head-to-head clinical studies based on biomarker-based patient stratification. Furthermore, data derived from large-scale, multi-center, real-world cohorts are also crucial for the establishment of predictive biomarkers, corroborating the findings of clinical trials. For example, a post hoc analysis has indicated that IL-22 positively predicts the efficacy of anti-IL23 agents [78]; however, this finding still needs to be corroborated by real-world data. Notably, it is crucial to emphasize the importance of establishing clear and consistent endpoint definitions across these studies. This standardization is essential for facilitating comparisons and ensuring the replicability of findings among different investigations. Moreover, from an ethical standpoint, the development and application of biomarkers must consider factors such as cost, accessibility, and other related issues, which underscores the particular importance of serum-based biomarkers. It is crucial to emphasize that although this review has shed light on the significant role of novel biomarkers in guiding therapeutic selection, other essential considerations—such as cost-effectiveness, the clinical profile of patients, and their personal preferences—must also be taken into account when determining the most appropriate therapeutic strategies in routine clinical practice.

In summary, there is considerable optimism that a key panel of biomarkers will be identified, realizing the tailored selection of biologics and small molecule drugs for IBD patients.

Author Contributions

L.C., C.Z. and R.N. contributed to the retrieval and filtering of studies included in this review. All authors contributed to the drafting and critical review of the manuscript content. R.F., Y.Q. and M.C. designed the study and obtained funding.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article are available in the article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.