

REVIEW

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Machine learning approach and internet of things technologies to unravel the complex interaction between microbiome-metabolome in inflammatory bowel disease: a new frontier in precision medicine

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Abstract

Inflammatory bowel diseases (IBD) are chronic, relapsing inflammatory disorders with ulcerative colitis (UC) and Crohns disease (CD) representing the two major phenotypes. While these conditions share common features, they exhibit distinct clinical presentations, disease behaviors, and pathogenetic mechanisms, highlighting the complexity of IBD. The global incidence and prevalence of IBD have risen dramatically in recent decades, probably linked to environmental changes such as dietary habits, urbanization, and reduced microbial exposure during early life, highlighting the interplay between environmental and genetic factors in disease pathogenesis. However, genetic factors alone cannot fully explain disease onset, emphasizing the critical role of environmental and microbial influences. Dysbiosis, characterized by reduced microbial diversity, loss of beneficial commensals, and an overabundance of pathogenic taxa, has emerged as a hallmark of IBD. Recent research has increasingly focused on the functional consequences of dysbiosis, its impact on microbial metabolites and pathways that contribute to chronic inflammation and disease progression. Understanding the functional implications of multi-omics changes, rather than simply cataloguing compositional changes, is now a priority in IBD research. Using artificial intelligence to combine data from noninvasive multi-omics technologies offers a significant opportunity to explore interactions among individual omics. It could represent a shift in IBD research by showing the complex mechanisms behind disease. This approach may revolutionize diagnostics and treatments, improving the quality of life for patients through precision medicine. This review aims to provide a comprehensive assessment of current progress. It highlights critical challenges and suggests possible future directions.

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Keywords Artificial Intelligence, IBD, Microbiome, Metabolome, Wearable devices

Introduction

Inflammatory bowel diseases (IBD) are chronic, relapsing inflammatory disorders that can affect any part of the gastrointestinal (GI) tract, with ulcerative colitis (UC) [1] and Crohns disease (CD) [2] representing the two major phenotypes. While these conditions share common features, exhibit distinct clinical presentations, disease behaviors, and pathogenetic mechanisms, underscoring the complexity of IBD as a spectrum of diseases rather than a single entity [3]. The global incidence and prevalence of IBD have risen dramatically in recent decades, particularly in newly industrialized countries [4]. This trend has been linked to environmental changes such as dietary habits, urbanization, and reduced microbial exposure during early life, highlighting the interplay between environmental and genetic factors in disease pathogenesis [5]. Despite advances in therapeutic development that have improved disease management, a definitive cure remains elusive, leading to significant morbidity, reduced quality of life, and increased healthcare costs [6]. IBD pathogenesis is multifaceted, involving a deregulated immune response to intestinal microbiota in genetically predisposed individuals [5]. However, genetic factors alone cannot fully explain disease onset, emphasizing the critical role of environmental and microbial influences. Dysbiosis, characterized by reduced microbial diversity, loss of beneficial commensals, and an overabundance of pathogenic taxa, has emerged as a hallmark of IBD. Recent research has increasingly focused on the functional consequences of dysbiosis, particularly its impact on microbial metabolites [7, 8].

Among the metabolites, short-chain fatty acids (SCFAs), such as butyrate, are essential for maintaining epithelial integrity and modulating anti-inflammatory responses. Similarly, secondary bile acids and tryptophan metabolites influence immune signaling and gut barrier function. Disruptions in these metabolic pathways contribute to chronic inflammation and disease progression [9].

Understanding the functional implications of microbiome alterations, rather than merely cataloging compositional changes, is now a priority in IBD research [8]. The integration of multi-omics technologies, including metagenomics, metatranscriptomics, metabolomics, and proteomics, offers a significant opportunity to explore the complex interactions between the microbiome and the metabolome [10, 11]. Despite these advances, several challenges remain, including high inter-individual variability, the complexity of managing large datasets, and the difficulty of extracting meaningful insights where

traditional methods or simple correlation models fail [12, 13].

From a clinical standpoint, several unmet needs persist, including the development of reliable biomarkers that can accurately predict disease onset, disease progression, flare-ups, and treatment response, enabling translational research and a personalized treatment strategy. Furthermore, current diagnostic and monitoring tools often lack the sensitivity and specificity required for early detection and optimal disease management [1–3].

In this context, artificial intelligence (AI) has emerged as an innovative tool for addressing these challenges. By leveraging AI, researchers can analyze large, multidimensional datasets to uncover hidden patterns and complex relationships [14]. AI-driven approaches enable the integration of data from various omics layers to predict disease onset, identify microbial and metabolic biomarkers, and stratify patients based on their response to therapy with greater accuracy, precision, and speed of investigation [15]. In particular, deep learning (DL) and network-based models hold great potential for modeling the intricate, multidimensional networks within the microbiome and metabolome interactions [16]. By facilitating a deeper understanding of the complex host-microbe-metabolome edges underlying disease pathogenesis, these approaches may revolutionize diagnostic and therapeutic strategies, ultimately improving the quality of life for IBD patients through precision medicine [3]. In addition, wearable devices, such as patches, smartwatches, wristbands, and rings, can support IBD management by capturing physiological and behavioral signals (e.g. sleep, activity, stress and diet) that influence intestinal barrier function and metabolic profiles. Combining wearable device data with biological analyses and AI could link physiological patterns to microbiome-metabolome changes and allow prediction of metabolomic fluctuations over time.

However, realizing this potential requires continued investment in interdisciplinary collaboration, robust data-sharing frameworks, and the development of AI tools that can be integrated into clinical workflows. The application of AI and computational methods to microbiome-metabolome research may represent a paradigm shift in the study of IBD.

Despite growing interest in AI applications in IBD, most existing reviews focus either on microbiome or metabolome analyses separately or provide only a general overview of AI in these complex diseases. There remains a need for a focused synthesis of how machine learning (ML) can help integrate microbiome-metabolome data

to better understand disease mechanisms and support clinical decision-making.

This review aims to provide a comprehensive evaluation of current advancements, highlight critical challenges, and assess the potential of ML approaches for integrating microbiome and metabolome datasets to identify patterns, biomarkers, and mechanistic pathways that can inform diagnosis, prognosis, and personalized treatment strategies in IBD.

Methods

We conducted a narrative review using Pubmed, Scopus, Web of Science, bioRxiv and Google Scholar from 2020 to march 2025. Six authors (O.P., A.L.C., A.L., L.M., F.B., F.U., and G.F.) independently conducted all literature searches, study selection, quality assessment, and data extraction according to a standardized protocol. Any discrepancies were resolved through discussion and consensus among them.

Our search included MeSH terms such as “inflammatory bowel disease”, “Crohns disease”, “ulcerative colitis”, combined with the Boolean operator “AND” to other MeSH terms such as “artificial intelligence”, “machine learning”, “deep learning”, “artificial neural networks”, “random forest” and “computer-aided systems, to focus on studies utilizing AI tools in IBD research. Additionally, to identify papers on integrative analysis and microbiome-metabolome interactions, we included terms such as “omics”, “microbiome”, “metabolome”, “multi-omics approach”, “multi-omics integration”, and “microbiome-metabolome interactions”. As an example, one of the Boolean search strings strategies employed in PubMed was: (inflammatory bowel disease) AND (artificial intelligence) OR (deep learning) OR (machine learning) AND (prediction) AND (microbiome—metabolome) to identify articles at(https://pubmed.ncbi.nlm.nih.gov/?term=%28inflammatory+bowel+disease%29+AND+%28artificial+intelligence%29+OR+%28deep+learning%29+OR+%28machine+learning%29+AND+%28prediction%29+AND+%28microbiome+-+metabolome%29&filter=dates.2020-2025%2F3&sort=date&sort_order=asc).

This strategy initially retrieved 146 records published in the last five years (from 2020 to 2025/3).

All studies involving patients with UC, CD or IBD were included, regardless of study design, number of participating centers and age group of the studied population (adults or pediatrics). There were no restrictions on sample size, or the type of AI strategy analyzed. After excluding duplicates, three reviewers (A.L.C., L.M., and F.U.) examined the abstracts for inclusion and exclusion criteria. Any disagreements were resolved by a fourth independent and experienced reviewer (O.P.).

The exclusion criteria were as follows: (1) studies on AI applications unrelated to microbiome-metabolome axis

analysis in IBD, such as those examining single-omics approaches, (2) non-English studies, (3) nonhuman studies, (4) case reports, (5) non-AI-enabled IBD models, (6) studies lacking extractable outcome data. Application of the predefined inclusion and exclusion criteria resulted in the final selection of 8 studies, which were narratively analyzed.

Artificial intelligence concepts

AI is a broad and interdisciplinary field that integrates concepts from computer science, engineering, philosophy, and linguistics to develop algorithms and models capable of learning from data and performing complex tasks that typically require human intelligence [17, 18]. One of AI's strengths is its ability to analyze large amounts of data in a short time and simulate how we understand, judge and predict things. To do this, the data must be correctly collected, electronically stored, and organized [19]. In medicine, AI has the potential to assist expert physicians in decision-making, uncover new features of multifactorial diseases, and identify novel biomarkers useful in diagnosis and treatment [20]. AI encompasses several subfields, with ML and DL being among the most prominent (Fig. 1).

ML is a branch of AI in which models learn from data to identify patterns and make predictions without explicit programming [21]. ML models improve performance by training on large datasets and refining their predictions based on learned interactions [19]. ML comprises three primary learning types: supervised learning, unsupervised learning, and reinforcement learning. Supervised learning trains algorithms on labeled data to predict known outcomes (e.g., linear regression, support vector machines (SVMs), and random forest (RF)) [22]. Unsupervised learning identifies hidden patterns in unlabeled data (e.g., hierarchical clustering and principal component analysis (PCA)) [23]. Reinforcement learning involves an AI system interacting with its environment and learning from feedback to optimize decisions over time [24]. DL is an advanced subset of ML that processes information using artificial neural networks (ANNs), interconnected layers of computational elements to analyze complex, multidimensional datasets [25]. Common architectures include convolutional neural networks (CNNs) for image and pattern recognition, recurrent neural networks (RNNs) for analyzing sequential data, and generative adversarial networks (GANs) for generating synthetic data and reducing dimensionality [26].

Artificial intelligence for multi-omic analysis in IBD

When studying microbiome-metabolome interactions in IBD, AI-based methods have proven highly effective. Supervised ML algorithms such as RF, SVMs, and ANNs classify IBD patients based on microbial and metabolic

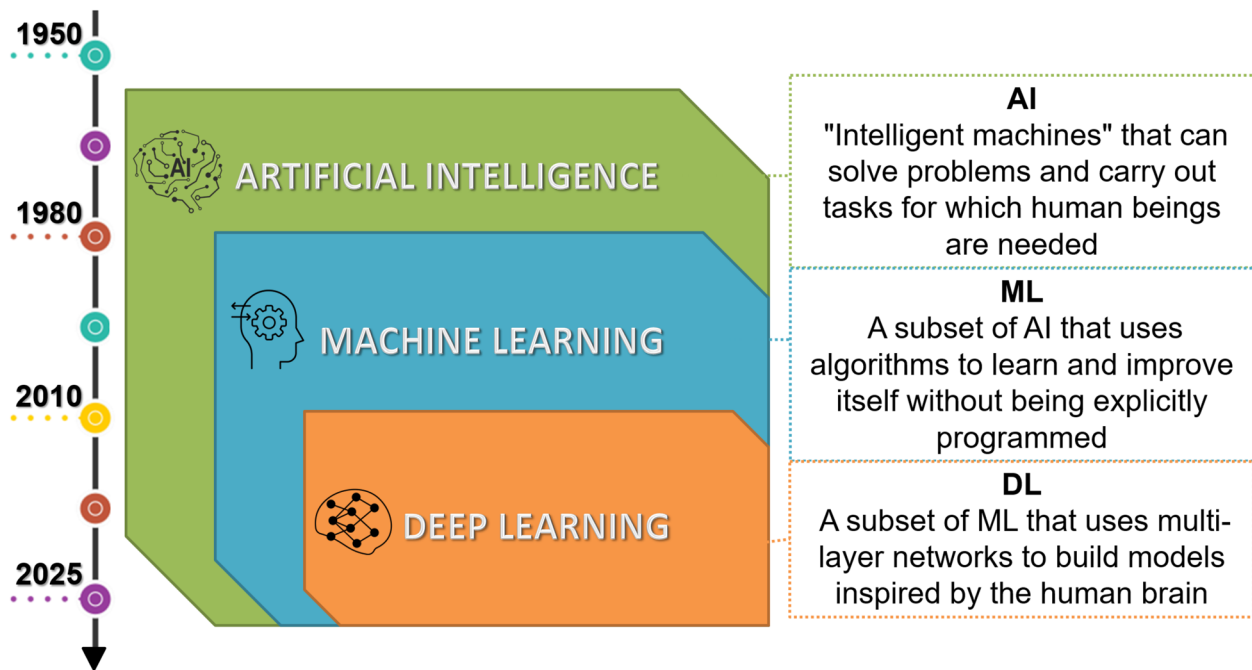


Fig. 1 Graphical representation of elementary concepts linked to artificial intelligence (AI) and their historical appearances. ML: machine learning; DL: deep learning

profiles, while unsupervised algorithms like hierarchical clustering identify patients subgroups based on microbial composition and metabolic characteristics [27]. Deep neural networks are often used for the integration of a wide variety of data and for the detection of patterns that traditional models may overlook. GANs have been used to simulate and predict metabolic responses based on microbial profiles [28], while autoencoders help reduce the dimensionality of multi-omics datasets without losing critical information [29].

Among the applications of AI in IBD, the integration and analysis of multi-omics data have enabled a better understanding of disease pathogenesis and the identification of diagnostic and therapeutic biomarkers [30]. Specifically, the role of AI on IBD microbiome-metabolome interactions can help to identify:

- Microbial-metabolite combinations associated with disease states or remission
- Estimation of disease severity, disease progression, risk of flare-ups and treatment response based on metabolic and microbial data
- Prediction of therapeutic response and personalized treatment strategies, such as dietary interventions, probiotics, and fecal microbiota transplantation (FMT) [31].

Several AI-driven multi-omics integration methods have been applied in IBD research, including Multi-Omics Factor Analysis (MOFA) [32], which integrates genomics,

metagenomics, and metabolomics data to identify hidden disease patterns. Bayesian network analysis has been used to model interactions between the microbiome, metabolites, and immune response [33], while sparse Canonical Correlation Analysis (sCCA) correlates specific microbial taxa with bioactive metabolites and inflammatory biomarkers [34].

Ai studies on microbiome-metabolome interactions in IBD

Table 1 summarizes the 8 most important studies that have investigated the AI models applied to study the interactions of the microbiome-metabolome in IBD patients.

Le V. et al. [29] were among the first to apply AI in microbiome-metabolome interaction analysis, developing a neural encoder-decoder network to predict metabolite abundances from microbial profiles. Using microbiome and metabolome data from Franzosa EA. et al. [35] (n=155 discovery cohort; n=65 validation cohort, including CD, UC, and non-IBD controls), they reduced metabolite clusters from 8848 to 143 classes and bacterial species from 201 to 51 genera via dimensionality reduction techniques. Their neural network, structured into microbe input, hidden (latent) layers, and metabolite output layers, outperformed linear models in microbiome-metabolome prediction, achieving a stability index of 0.79 when predicting metabolite abundance at the cluster level and 0.80 at the class level. An RF classifier trained on microbe-metabolite interactions

Table 1 Summary of key studies exploring AI models applied to study microbiome-metabolome interactions in IBD

AI studies on microbiome-metabolome interactions in IBD	AI classifier	Populations	Primary outcomes/Clinical results	Accuracy	Performance AUC	Stability index
Le V. et al. (2020) [29]	Neural encoder-decoder network	Discovery dataset: n=155 subjects (68 CD, 53 UC, and 34 HC); validation dataset: n=65 subjects (20 CD, 23 UC, and 22 HC)	Prediction of gut metabolites from the gut microbiome			0.79 when predicting metabolite abundance at the cluster level and 0.80 at the class level
Reiman D. et al. (2021) [36]	MiMeNet	Discovery dataset: 121 IBD patients (68 CD, 53 UC) and 34 HC, for a total of 201 microbes and 8848 metabolites; validation dataset: 43 IBD patients (20 CD, 23 UC) and 20 HC, for a total of 201 microbes and 8848 metabolites	Modeling of community metabolomic profiles using metagenomic taxonomic or functional features	SCC ranging from 0.25-0.41 in cross-validation and 0.14-0.28 in external validation		
Huang Q. et al. (2021) [37]	SVM; AdaBoost; RF; Multilayer perceptron	299 clinical cohort samples from the IBDMDB (86 HC, 140 CD and 73 UC)	Development of a diagnostic IBD model using multi-omic analysis		0.85 with 59 features (5 metatranscripts and 54 metabolites) and 0.84 with 22 features (3 metatranscripts and 19 metabolites)	
Lee J.W.J. et al. (2021) [38]	RF models	185 IBD patients (108 CD and 77 UC) at the start of anti-TNF (79 patients), anti-IL12/IL23 (21 patients) or anti-integrin (85 patients) therapy	Predicting treatment response		0.85 with clinical data and metagenomic features, 0.77 with clinical data and metabolomic features, 0.81 with clinical data and proteomic features, and 0.96 with clinical data and multi-omic analysis	
Yang S. et al. (2022) [39]	MB-SupCon	Discovery dataset: 720 samples from patients with type 2 diabetes; validation IBD dataset: 132 subjects (67 CD, 38 UC, and 27 HC)	Development of a microbiome-based predictive model integrating microbiome and metabolome data	0.74 to compare to approaches using original data directly		
Ning L. et al. (2023) [11]	RF model	Nine metagenomic cohorts (n=1363 cases), divided into six discovery cohorts and three validation cohorts; four metabolomic cohorts (n=398 cases), of which two external cohorts were examined using nontargeted metabolomics, and two in-house cohorts were examined using targeted metabolomics	Identification of bacterial species, KEGG orthology genes and metabolites that contribute to disease development		Ranging from 0.66 to 0.95 selecting 31 bacterial species; ranging from 0.74 to 0.81 selecting 25 KO genes; ranging from 0.84 to 0.94 selecting and 13 metabolites; ranging from 0.92 to 0.98 utilizing 31 bacterial species, 25 KO genes and 13 metabolites	

Table 1 (continued)

AI studies on microbiome-metabolome interactions in IBD	AI classifier	Populations	Primary outcomes/Clinical results	Accuracy	Performance AUC	Stability index
Arehart C.H. et al. (2024) [40]	LR models	1,785 repeat metagenomic, metatranscriptomic, viromic and metabolomic samples from the Human Microbiome Project 2 IBD multi-omic database: 103 IBD (65 CD and 38 UC) and 27 HC subjects	Prediction of IBD diagnosis		0.82 with metabolomics score; 0.83 with viromics score; 0.73 with metagenomics score; 0.73 with metatranscriptomics score; 0.80 with multi-omic analysis	
Hodgkiss et al. (2025) [13]	RF, XGBoost and LASSO	Discovery dataset: 164 patients with IBD (88 CD, 76 UC) and 56 HC, for a total of 11,720 genera and 8848 metabolites; validation dataset: 51 patients, 37 with IBD (16 CD, 21 UC) and 14 HC, for a total of 9,695 genera and 81,868 metabolites			0.92 using RF model and selection of 9 genera; 0.94 using RF model and selection of 14 metabolites; during validation: 0.62 using RF model e combining 9 selected genera and 14 selected metabolites; 0.58 using only microbe model; 0.50 using only metabolite model	

AI: artificial intelligence; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; HC: healthy control; AUC: area under the curve; SCC: Spearman correlation coefficient; SVM: support vector machine; RF: random forest; LR: logistic regression; IBDMDB: Inflammatory Bowel Disease Multi-omics Database; BA: bile acid

demonstrated that the latent space classifier performed comparably to the microbe-based classifier, suggesting that the microbe-metabolite axis itself represented an IBD-specific biomarker signature. However, when microbes and metabolites were used to discriminate patients from controls, similar performance with an area under the curve (AUC) value was achieved for microbes only, metabolites only, and microbes and metabolites (AUC>0.944) in CD vs. healthy controls (HC). For the classification of UC, good performance was obtained when considering only metabolites and microbes and metabolites together (AUC>0.930), whereas microbes only achieved a poor result (AUC=0.741). However, the studys use of non-negative weights may have constrained model learning capacity.

To address this limitation, Reiman D. et al. [36] introduced a Microbiome-Metabolome Network (MiMeNet), a multilayer perceptron neural network (MLPNN) modeling community metabolome profiles using metagenomic taxonomic or functional features. Three paired metagenomic-metabolomic datasets (IBD, cystic fibrosis, and soil wetting) and an external IBD dataset were used to evaluate the ability of MiMeNet. The first set of data was taken from a published study of patients participating in PRISM, including 121 IBD patients (68 CD, 53 UC) and 34 HC, for a total of 201 microbes and 8848 metabolites, used as a discovery set, and 43 IBD patients (20 CD, 23 UC) and 20 HC, for a total of 201 microbes and 8848 metabolites, used as an external validation set. MiMeNet demonstrated high predictive accuracy, with Spearman correlation coefficients (SCCs) ranging from 0.25–0.41 in cross-validation and 0.14–0.28 in external

validation. Although the values decreased in the external IBD data, the modules with the higher mean SCC in the cross-validated evaluation were also the modules with the higher SCC in the external IBD data. This demonstrates that the predictive ability and information carried by the collective members of each module were transferable to an external cohort of patients. Furthermore, using IBD data, the feature attribution scores derived from network weights can be used to construct modules of microbes with similar positive or negative effects on a set of metabolites. Moreover, the metabolite abundance values, and their module feature values are more predictive of IBD status (AUC~0.84) compared to the microbial abundance (AUC~0.76) and their module feature values, respectively. This demonstrated that MiMeNet can group microbes and metabolites with similar interaction patterns and functions to elucidate the microbe-metabolite interaction network.

Huang Q. et al. [37] developed an AI diagnostic model integrating six-dimensional fecal multi-omics data to stratify IBD and its subtypes. Using 299 clinical cohort samples from the Inflammatory Bowel Disease Multi-Omics Database (IBDMDB), including 86 HC, 140 CD, and 73 UC patients, feature engineering techniques selected 111 key features (96 metabolites, 15 metatranscripts). A DL model achieved high accuracy in patient stratification, with AUC values of 0.85, using 59 features including 5 metatranscripts and 54 metabolites, for individuals self-rating their health as “very good” and 0.84, using 22 features (3 metatranscripts and 19 metabolites) for those rating it “slightly below good.” The study highlighted the potential of non-invasive fecal sampling

to identify diagnostic biomarkers, potentially replacing colonoscopy and biopsy procedures.

Lee J.W.J. et al. [38] analyzed gut microbial composition in 185 IBD patients with moderate to severe CD or UC starting biologic therapy, and how these microbes might influence response. Multiple omics measurements were collected from 185 IBD patients, including 108 CD and 77 UC patients, at the start of anti-TNF (79 patients), anti-IL12/IL23 (21 patients) or anti-integrin (85 patients) therapy, with a total of 114 stool samples and 130 serum samples. The authors used linear modeling to relate microbial, metabolomic, and proteomic features to clinical outcomes. Baseline microbial richness indicated a preferential response to anti-cytokine therapy and correlated with the abundance of microbial species capable of 7 α / β -dihydroxylation of primary to secondary bile acids. Serum immune protein signatures reflecting microbial diversity identified patients more likely to achieve remission with anti-cytokine therapy. By building separate RF models with clinical data and metagenomic, metabolomic, or proteomic features, they achieved predictive values with AUCs of 0.85, 0.77, and 0.81, respectively. When clinical data were combined with all the multi-omics features the best prediction was achieved with an AUC of 0.96.

In 2022, Yang S. et al. [39] proposed a Microbiome-based Supervised Contrastive Learning Framework (MB-SupCon), a supervised learning framework for multi-omics datasets integrating microbiome and metabolome data. Applied to 720 samples with paired 16S microbiome and metabolomics data from type 2 diabetes and validated on an independent IBD dataset. Using the “diagnosis” of IBD status as the covariate, the approaches using MB-SupCon embeddings achieved significantly better average prediction accuracies (74.04%) compared to approaches using original data directly, including logistic regression (67.79%) and SVM (52.70%). This demonstrates the reliability and broad applicability of MB-SupCon. The authors concluded that their framework and neural network-based encoder, had advantages in approximating non-linear functions and modeling high-dimensional data, with potential applicability in broad multi-omics settings and improvement of microbiome-based prediction models.

Ning L. et al. [11] analyzed nine metagenomic (N=1363 cases) and four metabolomics (N=398 cases) IBD cohorts from different populations to identify bacterial species, Kyoto Encyclopedia of Genes and Genomes (KEGG) ortholog (KO) genes, and metabolites distinguishing HC from IBD cases. Initially, they developed an RF model incorporating 31 bacterial species that achieved AUCs ranging from 0.66 to 0.95. Subsequently, the authors, using several approaches, identified 25 KO genes that, for all cohorts, give AUCs ranging from 0.74

to 0.81, except for the HeQ 2017 (AUC=0.98). Using targeted metabolomics and a series of bioinformatics analyses, they identified 13 metabolites that were able to better outperform with AUCs ranging from 0.84 to 0.94. Therefore, they constructed multi-omics biomarkers for IBD diagnosis based on the RF model using 31 bacterial species, 25 KO genes, and 13 metabolites, which were validated in several global cohorts with AUCs ranging from 0.92 to 0.98. This provides valuable insights and an important resource for developing mechanistic hypotheses on host-microbiome interactions in IBD.

The aim of the study by Arehart C.H. et al. [40] was to develop a polygenic risk score framework using multiple omics data types to predict IBD diagnosis. Specifically, the authors used multi-omics data from the Human Microbiome Project 2 IBD multi-omics database, 1,785 repeat metagenomics, metatranscriptomics, viromics, and metabolomic samples from 103 IBD (65 CD and 38 UC) and 27 HC subjects to train and validate ML models. They used mixed effects, at least absolute shrinkage and selection operator regression, to select features for each omics, selecting 14 species, 23 pathways, 14 metabolites, and 6 viruses from the original datasets, generating separate single-omics prediction scores. When the single omics was analyzed, the metabolomics (AUC=0.82) and viromics (AUC=0.83) scores were individually more predictive than metagenomics (AUC=0.73) or metatranscriptomics (AUC=0.73) ones. This approach highlights the particular importance of the gut microbiome and complex phenotypes in a multi-omics context. The final regression model was able to predict IBD diagnosis with a multi-omics risk score of 0.80.

More recently, Hodgkiss R. et al. [13] aimed to identify the most important microorganisms and metabolites with differential abundance in fecal samples from individuals with and without IBD, using sophisticated ML and feature selection methods on the Franzosa E.A. et al. [35] dataset. After preprocessing the data, three different ML algorithms (RF, XGBoost, and LASSO) predicted the most important features. In the microbial analysis, 9 genera were selected in common across all algorithms, and the RF model performed best with an AUC of 0.92. In the metabolomic analysis, 14 metabolites were selected, and the RF model produced the highest AUC of 0.94. During the validation phase, the dataset was obtained from the HMP2 IBDMDDB database and consisted of 51 patients and samples, 37 with IBD (16 CD, 21 UC) and 14 HC. Three RF models were trained using only the 9 selected genera (model 1), only the 14 selected metabolites (model 2), and combining the two feature sets (model 3). Model 3 gave the best model performance (AUC=0.62), in contrast to the microbe-only model (AUC=0.58) and the metabolite-only model (AUC=0.50).

The brain-gut-microbiome axis through the use of wearable devices

More recently, the role of the brain-gut-microbiome axis in the pathogenesis and phenotypic expression of IBD has been compellingly explored using wearable devices capable of noninvasively and passively capturing physiological signals [41]. Wearable devices, including patches, smartwatches, wristbands, and ring devices, offer several advantages in IBD management. They enable continuous monitoring, providing a constant stream of real-time data that can help identify patterns or abnormalities indicative of impending flares. This dynamic view of the patients physiological state allows for earlier intervention, potentially reducing the risk of severe flare-ups and avoiding hospitalization [42].

Although still an emerging field of research, recent years have seen a growing number of studies focused on the application of wearable devices in the context of IBD.

In an initial study, activity and sleep data collected from wearable biosensors were used to predict the length of postoperative hospital stays [43]. Another study employed a home-based passive monitoring device to track changes in sleep, gait, and respiration. Using an ML approach, researchers were able to detect exacerbations in CD and correlate these metrics with the development of flare activity; the sensor predicted a disease flare accurately with an AUC of 0.80 [44].

Sweat sensors have shown promise in tracking inflammatory markers. For example, a sensor developed by Jagannath B. et al. [45] measured IL-1 β and C-reactive protein levels in 26 subjects, showing good agreement with standard reference methods. Two additional studies using wearable sweat-detecting devices demonstrated that sweat-based assessments of immune and inflammatory markers correlated well with serum measurements [46, 47]. The first study found that sweat TNF- α measurements differentiated subjects with active IBD from HC, with an AUC of 0.962. The other study found that a comparison of sweat measurements between active IBD and HC subjects distinguished an inflamed and uninfamed state, with an AUC of 0.85.

There is also growing interest in monitoring physiological stress parameters, given their negative impact on IBD progression by promoting intestinal inflammation through neuro-immune mechanisms. To date, wearable devices can monitor episodes of acute or chronic stress via heart rate variability (HRV), enabling researchers to study the relationship between stress and clinical exacerbations, and to analyze real-time physiological responses to stress in everyday life.

To demonstrate the feasibility of using wearable devices to monitor physiological metrics in relation to IBD disease activity, Hirten RP. et al. [48] conducted a pilot study in which 15 UC patients used a wearable patch measuring

HRV over 9 months. Subsequently, the same group [49] employed wearable devices such as Fitbit, Oura Ring, and Apple Watch in a cohort of 309 IBD patients (196 with CD and 113 with UC) to measure HRV, heart rate (HR), and resting heart rate (RHR). They found these metrics to be associated with both physiological and perceived stress and noted that changes in these measures preceded the onset of symptomatic flares. Specifically, physiological metrics were evaluated only for the Apple Watch and on a per-day basis (AUC of 0.98 at 49 days before flare) and on a per-hour basis (AUC of 0.99 at 49 days before flare). This research highlights the potential of wearable technology in the early detection of IBD flares and in sensing early signs of autonomic dysfunction.

Discussion

While AI is transforming many areas of biomedical research, its application to microbiome-metabolome interactions and their modulation by environmental exposure monitored by wearable devices, remains an emerging and relatively unexplored field in IBD. The complexity of these interactions, the high-dimensional nature of multi-omics data, and the variability across different cohorts and populations have made it challenging to develop robust models to further enhance diagnostic performance. However, AI is increasingly being used to enhance our understanding of IBD pathogenesis, to identify biomarkers for diagnosis and disease progression, and to predict treatment responses. In the near future, it may also provide new insights into microbe-metabolite interactions (Fig. 2). This narrative review drew upon multiple open-access research databases; however, it did not include IEEE Xplore or arXiv, which may introduce selection bias. In view of its scope and inherent limitations, future research should pursue systematic meta-analyses to provide more comprehensive and quantitative evaluations, helping to mitigate such bias. As highlighted in our review, AI is primarily applied to microbiome-metabolome interactions for three main purposes:

- Predictive modeling: AI is used to infer metabolite abundance from microbial composition, helping to characterize the functional consequences of microbiome alterations in IBD.
- Biomarkers identification: AI-driven feature selection methods help identify key microbial and metabolic biomarkers associated with the disease, offering new insights into potential therapeutic targets.
- Multi-omics integration: AI enables the development of comprehensive models that combine metagenomic, metabolomic, and proteomic data to improve diagnostic accuracy and patient stratification.

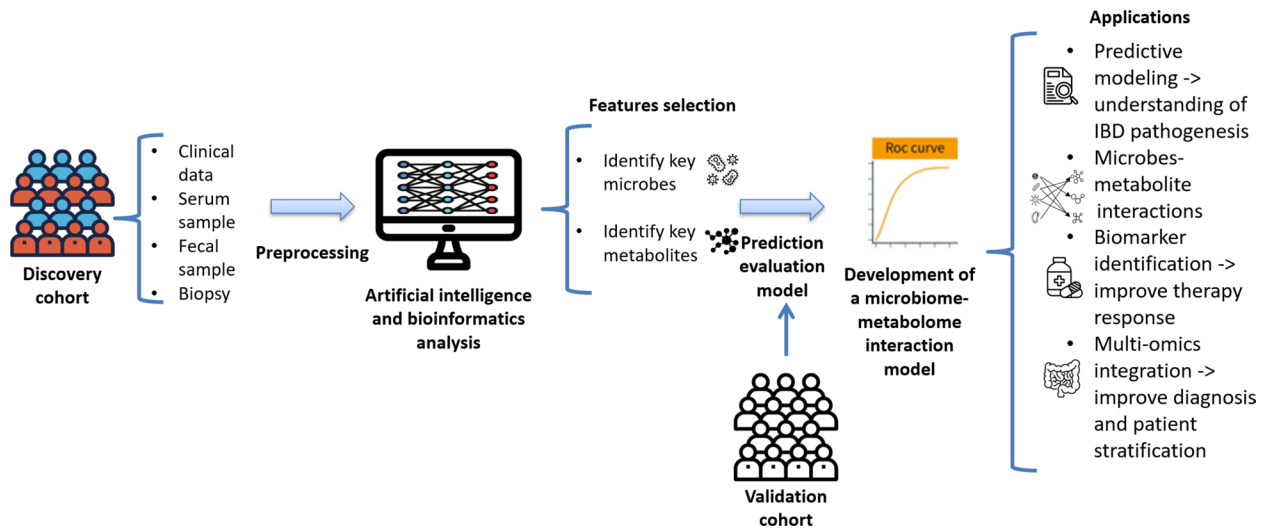


Fig. 2 Schematic workflow for developing an AI model of microbiome-metabolomics interactions and its applications. The workflow starts by collecting various data from the discovery cohort. After preprocessing, AI techniques analyze the data to select optimal features for model development and training. Next, the model is validated using new, unknown data obtained from a validation cohort to assess its performance. This process helps develop a model of the interaction between the microbiome and the metabolome that can improve future understanding of IBD. AI: artificial intelligence; IBD: inflammatory bowel disease

Among the studies published in this field, early efforts by Le V. et al. [29] and Reiman D. et al. [36] focused on the identification of predictive modeling to predict metabolite abundance based on microbial profiles. While Le V. et al. [29] demonstrated the feasibility of such models, their approach was limited to using non-negative weights, which restricted flexibility. Reiman D. et al. [36] addressed this issue with MiMeNet, a more adaptive neural network that improved prediction accuracy. However, both studies faced challenges with model generalizability, as their predictive performance often declined when tested on external datasets.

Other studies, such as those by Hodgkiss R. et al. [13] and Ning L. et al. [11], applied ML-based feature selection approaches for biomarkers identification. Hodgkiss R. et al. [13] achieved high accuracy within their dataset by leveraging multiple algorithms to pinpoint key features. However, their models performance decreased on external datasets, raising concerns about overfitting. Ning L. et al. [11] tackled this issue by incorporating multiple global cohorts, demonstrating that while AI models can achieve high diagnostic accuracy, regional differences in microbiome composition can impact performance. These findings underscore the need to train AI models on heterogeneous datasets to improve robustness.

The multi-omics integration data represents another significant advancement. Huang Q. et al. [37] and Arehart C.H. et al. [40] incorporated microbiome, metabolome, metatranscriptome, and proteome data into their models to enhance IBD classification. Huang Q. et al. [37] showed that non-invasive fecal samples could potentially replace invasive diagnostic procedures, while Arehart

C.H. et al. [40] found that metabolomics and viromics were more predictive of IBD than metagenomics. Similarly, Lee J.W.J. et al. [38] explored microbiome-metabolome relationships in relation to treatment response, demonstrating that patients with specific microbial and metabolomic profiles responded better to biologic therapies. These studies highlight the potential of AI to integrate diverse data for improving both diagnosis and personalized treatment strategies. Beyond disease classification, some studies have focused on disease progression. Yang S. et al. [39] developed a contrastive learning framework to improve microbiome-based phenotype prediction using metabolomic data, further emphasizing AI's potential in disease modeling. However, as with previous studies, external validation remained a major challenge.

Common limitations across studies

Despite these advancements, common limitations had emerged across studies analyzed. These obstacles must be overcome before AI can be fully integrated into microbiome-metabolome research. One of the most pressing issues is model generalizability. Many AI models perform exceptionally well within a given dataset but struggle to maintain accuracy when applied to external cross-cohorts. This is partly due to variations in microbiome composition influenced by geography, diet, and genetics, as well as differences in data collection and processing techniques including preprocessing pipeline and sequencing depths.

Additionally, most AI models are trained using relatively small sample sizes, and homogeneous datasets

which are imbalanced as compared to real-world data. This limits their ability to capture the full spectrum of host-microbe-metabolite interactions, resulting in low interpretability.

Addressing this issue requires larger, external datasets and more diverse datasets based on real-world experience, as well as multi-center collaborations to ensure that AI models are reliable across different patient populations.

The related issue of overfitting is another challenge. While complex AI models may appear highly accurate during training, they often fail when tested on new data. In fact, in some papers reported here, although the AUC values in the training set were excellent with scores more than 0.98, in the validation set, they failed (AUCs > 0.62) by using multi-omics approaches. Currently, none of the analyzed studies provide results on the external validation set. This represents a further bias that we hope will be investigated in the future. Conversely, simpler models may underfit due to the intricate relationships present in multi-omics data. Another major limitation is the interpretability of AI models. While DL techniques can uncover complex patterns, they often function as “black boxes,” making it difficult to extract biologically meaningful insights. In the context of microbiome-metabolome interactions, this lack of interpretability is particularly problematic, as understanding the mechanistic links between microbial and metabolic changes is critical for translating AI findings into clinical applications.

Privacy and data security are also critical concerns, particularly given that AI models rely on large-scale patient datasets. Ensuring compliance with data protection regulations while enabling meaningful data sharing for AI training is a delicate balance.

While AI has the potential to merge multi-omics data into more comprehensive disease models, the variability of sample handling, the platforms used for the omics analyses, the different quantification methods employed, and the lack of standards for data formats and analysis pipelines make it difficult to compare results across studies. This hampers reproducibility and remains a challenge for the future.

Finally, interdisciplinary collaboration will play a pivotal role in overcoming these challenges. AI-driven microbiome-metabolome research must integrate expertise from computational biology, gastroenterology, microbiology, and bioinformatics to develop clinically relevant models.

Future integration of microbiome, metabolome and wearable-derived metrics

Future efforts should advance AI models that capture the complex microbe-metabolite-environment interplay, whether through linear scaling of microbial abundance to

metabolite levels, dominant-species frameworks attributing metabolites to key taxa, multiview approaches disentangling environmental effects, or latent-variable models representing host-specific bidirectional steady states. Crucially, these models must be accurate, generalizable, interpretable, and clinically actionable [50].

Although no studies have yet directly examined microbiome-metabolome interactions in IBD using wearable technologies, research is advancing in promising directions that may lead to such integration in the future. The combined use of wearable devices for physiological monitoring and advanced sensors for multi-omics analysis could offer a more comprehensive and personalized approach to IBD management. A future goal may be the development of an integrated system capable of simultaneously studying microbiome, metabolome, longitudinally collected physiological wearable-derived metrics (i.e. heart rate, resting heart rate, heart rate variability, steps, and oxygenation) and environmental in patients with IBD.

In fact, if wearable devices monitor data and integrate effective AI algorithms, they could help identify an early flare, adapt a patient's diet, or adjust therapy according to their microbiome and metabolome characteristics. Currently, the use of these devices in studying microbiome-metabolome interactions has several limitations, such as great biological variability between patients, which makes generalizing data difficult, and the absence of sensors capable of directly measuring what is happening in the gut. These sensors are based on signals whose clinical validity is not yet fully proven. Other obstacles include the lack of standardized protocols for interpreting the collected data, the devices lack of official recognition as medical instruments, and limited patient access to these technologies, primarily due to economic, older adults or individuals with limited access to technology. Thus, wearables are a promising prospect for studying IBD from a personalized perspective. However, to be integrated into clinical practice, technical, regulatory, and scientific challenges must be overcome. By fostering collaboration between data scientists and clinicians, AI can be leveraged not only for biomarker discovery but also for improving patient stratification, treatment personalization, and disease monitoring. Only by addressing these challenges can AI truly transform microbiome-metabolome research into a practical tool that enhances both scientific discovery and patient care.

Conclusions

AI is emerging as a powerful tool for unraveling microbiome-metabolome interactions in IBD, with significant potential to improve biomarker discovery, patient stratification, and microbiome-based therapies. By integrating multi-omics data, AI can help identify key microbial

species and metabolic signatures associated with treatment success, particularly in therapies such as FMT. This could enable the selection of optimal donor profiles and the development of personalized treatment strategies, ultimately enhancing FMT efficacy by targeting specific microbial compositions associated with positive clinical outcomes. However, several challenges must be overcome before AI-driven insights can be translated into clinical practice, with the hope that the use of wearable technologies will be able to identify patterns or abnormalities indicative of impending flare-ups. Model generalizability, interpretability, and data standardization remain significant hurdles. To overcome these limitations, future efforts should focus on developing robust validation frameworks, enhancing model interpretability, establishing standardized multi-omics data integration pipelines, and encouraging interdisciplinary collaborations or longitudinal studies to bridge the gap between AI research and clinical application. By addressing these challenges, AI has the potential to revolutionize precision medicine in IBD, offering more accurate diagnostics, personalized therapies, and improved patient outcomes.

Author contribution

A.L.C., O.P., F.P., S.D. and F.U. Study design and data analysis and final approval of article; A.L.C., O.P., F.B., L.M., A.L., S.C., G.F., A.L.P. DB., M.G. and M.R., data collection and writing up of the first draft of the paper, and final approval of the article.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

S.D. has served as a speaker, consultant and advisory board member for Schering Plough, Abbott (AbbVie) Laboratories, Merck and Co, UCB Pharma, Ferring, Cellierix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alfa Wasserman, Genentech, Grunenthal, Pfizer, AstraZeneca, Novo Nordisk, Vifor and Johnson and Johnson. The other authors declare no potential conflicts of interest.

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