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**Integration and implementation of precision medicine in the multifaceted inflammatory bowel disease**

Jagirdhar GSK *et al*. IBD and precision medicine

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**Abstract**

Inflammatory bowel disease (IBD) is a complex disease with variability in genetic, environmental, and lifestyle factors affecting disease presentation and course. Precision medicine has the potential to play a crucial role in managing IBD by tailoring treatment plans based on the heterogeneity of clinical and temporal variability of patients. Precision medicine is a population-based approach to managing IBD by integrating environmental, genomic, epigenomic, transcriptomic, proteomic, and metabolomic factors. It is a recent and rapidly developing medicine. The widespread adoption of precision medicine worldwide has the potential to result in the early detection of diseases, optimal utilization of healthcare resources, enhanced patient outcomes, and, ultimately, improved quality of life for individuals with IBD. Though precision medicine is promising in terms of better quality of patient care, inadequacies exist in the ongoing research. There is discordance in study conduct, and data collection, utilization, interpretation, and analysis. This review aims to describe the current literature on precision medicine, its multiomics approach, and future directions for its application in IBD.

**Key Words:** Precision medicine; Multiomics; Inflammatory bowel disease; Crohn’s disease; Ulcerative colitis; Data integration

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**Core Tip:** Precision medicine holds significant promise in managing inflammatory bowel disease (IBD) by aiming to customize treatments based on the unique biological characteristics of patients. Despite advancements in biological and small-molecule therapies offering new therapeutic options for IBD; however, the is a large gap in understanding the clinical course of IBD, the durability of treatment response, and enhancing available and new therapeutic options. Integrating multiomics into patient care can help in early diagnosis, predict disease course, deliver targeted treatments based on unique patient profiles, and evaluate prognosis.

**INTRODUCTION**

Understanding precision medicine requires knowing two important concepts. (1) The definition of precision medicine; and (2) The role it plays in inflammatory bowel disease (IBD).

According to the National Cancer Institute, precision medicine is a form of therapy that utilizes knowledge about an individual’s genetic makeup or specific proteins to prevent, diagnose, or treat diseases[1]. Liu *et al*[2] state the term was first proposed in 2011, and over the years, this term has gained more importance. The strategy of precision medicine is to classify patients with shared characteristics into the same subgroup based on specific and similar clinical features, treatment, and prognostic factors[2].

The pathophysiology of ulcerative colitis (UC) and Crohn’s disease (CD) is increasingly evolving, mainly focusing on its genome, exposome, microbiome, immunome, and many other omics approaches. Thomas *et al*[3] noted that the development of IBD is attributed to an aberrant immune reaction resulting from intricate interactions among various genetic risk factors, imbalanced gut flora, and environmental influences. Unlike rare and clearly defined monogenic disorders, IBD arises from mutations in multiple genes rather than a single gene[3]. In this sense, precision medicine is pivotal in creating personalized therapies combining these various aspects into a multiomics approach[4]. If we target only the immune part of it without addressing the genome, the microbiome can result in treatment-limited success[2]. By treating IBD patients with the same and limited therapies, we assume that the underlying gastrointestinal inflammatory process is the same in all patients. Precision medicine in IBD aims to utilize specific clinical and biological characteristics of patients to predict disease and therefore use the correct treatment at the right time for the right patient[5].

The three priority areas of the precision medicine approach to IBD are (1) understanding the vulnerability, severity, and behavioral aspects of disease; (2) forecasting the response to medications; and (3) enhancing existing and creating novel molecular technologies to facilitate precision medicine.

We can achieve this through advances in multiomics in IBD. Figure 1 shows the various omics in IBD management. Using this approach, we could better understand disease pathogenesis, model predictive biomarkers, and facilitate early diagnosis and treatment.

**Literature search**

We conducted a review of existing literature in PubMed and Google Scholar to find relevant studies with information on multiomics in IBD and integrating various IBD therapies. We included studies from inception to May 2023. We created search criteria using a combination of free text words, including precision medicine, IBD, Genome, epigenome, epigenetics, proteome, transcriptome, immunome, microbiome, and integration. We examined studies that were published in the English language as part of our review. Pertinent articles were analyzed and incorporated into the review.

**Genomics**

Genetic factors stratify IBD into UC and CD. The utilization of genome-wide association studies (GWASs) has enabled the identification of notable genetic risk regions and IBD phenotypes to classify the disease into ileal Crohn’s, colonic Crohn’s, and UC compared to the current classification[6]. The genetic mechanisms implicated in IBD encompass various pathways, including microbial sensing (*NOD2, CARD9* and *RIPK2*), maintenance of intestinal barrier function (*C1orf106* and *HNF4A*), signaling within the innate and adaptive immune systems (*NLRP7, IL18RAP, CD28, IFNG, PTPN22, STAT4, IL6ST, IL23R, RORC and IL17RA*), fibrosis development (*OSMR* and *SMAD3*), and cellular homeostasis (*ATG16L1, RNF186* and *ERGIC1*)[7]. Despite the advances in genetic pathways, few relate to treatment response, prognosis, or clinical outcomes. Over 230 genetic loci have been identified to be involved in IBD[2,6,8]. However, in one of the largest phenotype-genotype GWASs of 29838 patients by Cleynen *et al*[6], over 163 loci related to IBD were studied, and genetic risk scores were created for CD and UC separately. On cross-validation of the data, the predictive accuracy for phenotypic variance in the adult population was low. These genetic predictors, along with smoking, could only explain 6.8% of the disease location with CD and only 1.1% with UC emphasizing that research using an interdisciplinary approach is required to provide the best risk assessment and aid diagnosis[6].

GWASs have been used in investigating pathways like the *NOD2/CARD15*, which are involved in pattern recognition and receptor signaling in response to microbial signaling. It has been associated with an ileal fibrostenotic disease phenotype that needs surgery and has a complicated disease course[9]. There is another study of the ATG16L1, T300A, an autophagy pathway reported to give an enhanced risk of CD[10]. Another autophagy gene *IGRM* is associated with penetrating disease in CD[11]. Interleukin (IL)-3 receptor has become a therapeutic agent for CD[12]. Studies have utilized genome basis to identify patients that benefit from hematopoietic stem cell transplantation (HSCT) and mesenchymal stem cell transplantation in patients with early-onset IBD and those with inborn errors of immunity[13-16]. Patients with genetic deficiencies such as IL-10, IL-10 receptor, and *XIAP* deficiencies benefitted from HSCT[13,17,18]. It also identifies mutations such as *STXBP2, TTC7A*, and *EPCAM* genes that will not benefit from particular therapies[19-21]. IBD is a polygenic disease, and research on the utilization of genome pathway-specific therapies to correct genetic defects is still developing. Thus, understanding genetic mechanisms helps personalized medicine in IBD.

**Epigenomics**

Epigenetics is the study of inheritable changes in gene expression that are not caused by alterations in the DNA sequence.

Environmental factors cause alterations in DNA methylation, histone modifications, and miRNA synthesis, thus changing the phenotypic expression of genes and response to treatment. Parenteral exposure influences epigenetic alterations that are transmissible across generations. Epigenetics factors are potentially modifiable and preventable. Maternal protein restriction and maternal high fat intake were associated with DNA methylation changes that led to increased steatosis, impaired glucose tolerance, diabetes, and obesity in offspring[22,23]. Pan *et al*[24] describe gut microbiota alteration that causes changes in DNA methylation and transcriptome changes in intestinal epithelial cells postnatally in newborns[24]. A prospective study by Sun *et al*[25] describes a 12-year follow-up of CD and UC patients. Patients with unhealthy lifestyles had a hazard ratio (HR) of 1.94 and 1.98 for CD and UC. Patients with increased genetic risk for IBD but healthy lifestyles had a lower risk of developing IBD than those with increased genetic risk and unhealthy lifestyles (HR: 2.23 *vs* 4.40)[25]. Yang and Jostins-Dean[26] published data using the information of IBD patients from a United Kingdom biobank. They analyzed 24 dietary exposures, perinatal childhood exposures, and lifestyle factors in individuals. They showed that multiple factors interacted, causing polygenic risk in predicting IBD occurrence. Factors such as appendectomy, smoking, childhood antibiotic use, exposure to the sun in winter, socioeconomic factors, and oral contraceptive use played a role in IBD pathogenesis[26]. Ryan *et al*[27] found that inflamed and non-inflamed colonic mucosa in IBD patients had different microbiota composition and epigenetic profiles. Using machine learning to classify disease status and inflammation, the authors found that epigenomics and microbiota could classify UC, CD, and health status with an AUROC of 0.87[27]. Thus, epigenetics plays a role in defining IBD risk.

**Exposome**

The exposome is defined as all encountered exposures in the lifetime of an individual beginning from conception. There are endogenous and exogenous exposomes in IBD. Microbiota is an endogenous exposome. Evidence suggests that mode of delivery at birth (cesarean *vs* vaginal, breastfeeding *vs* formula feeding) and early exposure to antibiotics in life are associated with intestinal colonization of bacteria early in life[28,29]. They contribute to intestinal immune homeostasis and are associated with UC and CD development[28]. Direct effects of infections, stress, diet, air and water pollutants, food additives, antibiotics, vitamin D deficiency, and physical activity on intestinal mucosal cells and indirect effects through alterations in the microbiome and immunomodulation influence IBD occurrence, presentation, course, and response to treatment[30,31]. These factors have been shown in animal models to induce DNA methylation and alteration in RNA and histone proteins, promoting the development of IBD[31]. Notably, Borg Bartolo states that industrialized nations exhibit the highest incidence of IBD[4]. According to Lamb *et al*[32], it is the environmental factors that influence IBD pathogenesis. A western diet of fast and processed foods, high-fat content, ultra-processed food consumption, and meat increases the risk of developing disease. In contrast, mitigating elements comprise elevated consumption of dietary fiber, caffeine, fruits, vegetables, olive oil, seafood, cereals, and nuts; all of which play a crucial role in safeguarding against certain conditions[32]. Initial investigations have demonstrated that exclusive enteral nutrition (EEN) diets based on specific formulas can effectively trigger remission in individuals with CD. As per the findings of Svolos *et al*[33], a customized food-based diet has been developed, sharing a similar composition with EEN. This personalized diet has exhibited favorable tolerability, notable enhancements in disease activity, significant alterations in the gut microbiome, and a metabolome profile comparable to that achieved with EEN[33]. Smoking, for example, is a risk factor in the progression of CD[34]. The relationship between IBD and smoking varies for CD and UC. Chemicals contained in the smoke generate carcinogenic and mutagenic components that can affect the immune system in the gastrointestinal mucosa. Smoking releases reactive metabolites that can cause DNA methylation, thus affecting gene regulation and expression[28]. Epigenome and exposome are closely interlinked in IBD pathogenesis.

**Immunome and proteome**

The gut is the main barrier that controls the immunological interface and maintains the immunological balance by appropriately recognizing and tolerating bacteria, food antigens, and self-antigens. Proteomics studies can develop targeted therapy for IBD and find biomarkers to monitor drug response in IBD patients. Yau *et al*[35] describe that blood tests can identify epithelial component proteins that help in early predicting intestinal complications in IBD, such as stricturing and fistulizing disease[35]. Deeke *et al*[36] describe the identification of active IBD and pancolitis based on a panel of proteins in IBD stool samples[36]. IBD tissue samples can be classified into UC or CD based on proteomic analysis[37-39].Protein analysis also helps to understand the response to treatment therapies[40]. Calprotectin is a marker that can be used for mucosal healing and clinical remission in IBD[41,42]. Tumor necrosis factor-like ligand 1A (TL1A) is involved in colonic inflammation and fibrosis through epithelial-to-mesenchymal cell transition and immune response mechanisms. It was detected in high levels in IBD patients. This is a potential target for IBD treatment[43]. Since IBD is an immune-mediated disease, both CD and UC have primarily immune targets for treatment. Masoodi *et al*[44] described altered polyunsaturated-fatty-acid-derived lipid mediators (eicosanoids), such as PGE2, PGD2, TXB2, 5-HETE, 11-HETE, 12-HETE and 15-HETE, that are elevated in inflamed mucosa in IBD patients and correlated with the severity of inflammation. These can assist in diagnosing inflammation in IBD[44,45]. Bennike *et al*[46] describe increased levels of neutrophils and neutrophil extracellular traps and several other proteins in UC patients’ normal-appearing colon tissue, suggesting the role of innate immune system in IBD[46]. Titz *et al*[45] identified 18 studies on proteomics and lipidomics to identify biomarkers for IBD. Through the utilization of blood, serum samples, and colonic mucosal biopsies, these studies aided in diagnosis, patient stratification, treatment categorization, and response[45].

**Microbiome**

The microbiome is a critical factor in initiating and perpetuating the inflammatory response of IBD. Studies conducted on patients initiating treatment with vedolizumab have observed a higher prevalence of *Roseburia inlinivorans* and a species belonging to Burkholderiales among individuals with CD who successfully achieved remission by week 14[47]. Furthermore, a study indicated that neural networking modeling demonstrated superior predictive capability for remission when utilizing microbial metadata compared to relying solely on clinical metadata. In 232 patients in the CERTIFIED study treated with ustekinumab, *Faecalibacterium* and *Bacteroides* were found in baseline stool in CD patients who achieved remission[47]. Microbiome has also helped identify high-risk individuals. Gevers *et al*[48] discovered that specific microbial patterns in the ileum could accurately predict the occurrence of CD, even in cases where inflammation was not present[48]. Vázquez-Baeza *et al*[49] describes that microbes play an important role in altering the response to medications, indicating that altering them could modify a patient’s response to treatments. This can be a future target in microbiomics research[49].

Precision medicine needs to be applied by taking each of the above aspects and unifying them. The concept is to integrate data and generate patient profiles that could predict disease risk, onset, progression, complications, prognosis, and treatment in multi populations based on multiomics. Figure 2 describes a simplified pathway for utilizing multi-omics in IBD.

**Precision medicine to predict disease susceptibility, diagnosis, and clinical phenotype**

The true power of precision medicine resides in the vast possibilities presented by multiomics data and its ability to merge effectively with clinical information. This concept is already applied in the field of oncology, where accurate biomarkers are utilized to forecast prognosis and anticipate the response to treatment[10]. The field of medicine has shifted from a treatment-oriented approach to a personalized and preventive approach. Biological data acquisition and digitization techniques have advanced, producing large amounts of high-specificity data. To examine and interpret these data, new databases, algorithms, and user-friendly applications are being designed to facilitate the analysis by bioinformatics specialists and physicians[5,50]. Table 1 shows studies utilizing multiomics in IBD for diagnosis and treatment.

To enhance transparency and accessibility of bio-sample data, standardization and harmonization of data frameworks are needed at a global level. A Data Commons should be established to facilitate global collaboration and provide access to biospecimens and data before and after treatment with established and novel therapies[3,51].

Cleynen *et al*[6] conducted a large genotype association study in patients with IBD using genotype-phenotype associations from 156-154 gene variants. They found ileal CD, colonic CD, and ulcerative colitis as distinct groups based on genetic risk scores of 29 838 patients. The application and utilization of these groups in clinical practice and patient treatment is not yet studied in detail[6]. Epigenetic studies by authors like Sun *et al*[25] prove the importance of genome-wide associations and gene–environment studies in IBD[25]. There is a need for biobanks such as the Dutch IBD biobank[52] and the GETECCU Eneida registry to be established globally since genetic predisposition, varied environmental exposures, and population differences can create different genetic susceptibilities based on location[53]. These can create population-specific effects that are not generalizable to all IBD patients[28]. This will create patient profiling that can be distinct based on geographic location. Studies conducted using biobank information also need to be standardized with quality control and the establishment of core validation guidelines so that generated results are comparable across studies and can be utilized to further precision medicine in IBD. Multiple studies analyzing biomarkers in IBD have been published, but the results have not been translated to clinical practice. We are lagging in terms of translation of the discovered research[45].

Screening programs such as DNA or RNA sequencing can inform healthy people with a family history of cancer about their health status. For example, mutations in the BRCA genes can be detected to identify the familial risk of breast cancer[54]. Disease monitoring using a combination of clinical data, biomarkers, imaging, therapeutic drug monitoring, modeling, and simulation is essential. The objective is to administer the appropriate treatment to each patient precisely when it is needed, based on their unique disease pattern and progression. By doing so, aiming to minimize long-term complications and improve patient outcomes[55]. The ability to identify the correct personalized therapies should also result in an earlier clinical response compared to current treatment strategies.

Omics are fields of study that analyze biological molecules and systems on a large scale. They aim to understand the complex interactions and functions of these molecules and systems and how they contribute to the health and disease of organisms. The study of genomics and transcriptomics is crucial for discovering disease pathways and designing effective drugs. Understanding these areas can help treat diseases that do not respond to current treatments. Nucleic acid sequencing methods, particularly next-generation sequencing technologies, are essential for studying genomics and transcriptomics. Various studies have explored individual differences in patients with the same condition at the genome level, including the human genome project, single nucleotide polymorphism detection, and GWASs. For the transcriptome, splicing, alternative splicing, and RNA sequencing are critical areas because many human genes undergo alternative splicing, and changes at this level can be difficult (and usually impossible) to detect at the genome level[54].

IBD omics investigate particular characteristics associated with IBD, emphasizing the importance of using methods that thoroughly explore and model the various interactions at play, enabling the acquisition of comprehensive knowledge. The use of molecular markers or molecular disease profiles can eliminate the interpretive aspects of response and remission definition and can guide more accurate drug selection and monitoring of immune modulators, biologics, and small molecule therapy[3,51,56].

The primary obstacle in the development and validation of precision medicine interventions for IBD lies in the extensive variability observed in disease progression, coupled with the current inability to accurately predict its course. Predictive models need to account for environmental influences and the heterogeneous response to treatment over time. Although mucosal healing serves as a substantial indicator for predicting future relapse, complications, and the likelihood of surgery, the requirement for frequent endoscopic examinations can be resource-intensive and may not be well-received by patients. To address this, patient-reported outcomes, and noninvasive biomarkers like fecal calprotectin (FC) and C-reactive protein (CRP) are highly utilized to assess treatment response in both research studies and clinical practice. However, the lack of universally agreed-upon definitions for treatment response and remission poses challenges in interpreting the usefulness of these measures[4,32].

A systematic analysis of six studies showed that two consecutive elevated FC levels predicted disease relapse within the next 2-3 mo, but an optimal cutoff for monitoring could not be defined. However, it was discovered that setting a cutoff value of no more than 250 μg/g for FC could effectively predict the achievement of endoscopic remission. Likewise, it was observed that CRP exhibits a correlation with both clinical disease activity and endoscopic inflammation. However, it is important to note that CRP levels can also be elevated in other clinical situations, such as infections. Glycoprotein acetylation (GlycA) is a new biomarker that has been investigated as a potential disease activity biomarker in patients with IBD. GlycA presents a potential advantage over CRP due to its composition as a composite marker derived from various acute-phase proteins. This characteristic renders GlycA more stable compared to CRP[4].

Two studies in 2021 shed light on the development and treatment of IBD[50]. The first study investigated the role of *NOD2* variants in the pathogenesis of CD and found that loss-of-function mutations in *NOD2* were associated with the activation of a macrophage–fibroblast niche, which is involved in the development of the disease. The study also identified a potential signaling pathway involving the gp130-STAT3 axis, which may contribute to the pathogenesis of CD. Furthermore, the study found that the gp130 inhibitor bazedoxifene could alleviate pathogenicity in zebrafish models of IBD. The second study aimed to predict the effectiveness of treatments for patients with IBD by analyzing microbial community profiles, baseline clinical features, and serum inflammatory markers. The study found that patients who started with anticytokine therapy had higher remission rates compared to those who began with anti-integrin therapy. Additionally, the study demonstrated the potential for using multiple types of data, including metagenomic, metabolomic, and proteomic features, to predict therapeutic efficacy for patients with IBD[5,50].Rapid advances in human microbiome research suggest that profiling and manipulating the human microbiome can offer significant opportunities for diagnosis, intervention, risk management, and risk stratification[2].

Discussions about the integration of research and clinical care have focused more on human genetic and genomic data than human microbiome data. In 2014, working groups were established to explore the storage and display of genetic information in electronic medical records, which revealed differences in how genetic information was documented across institutions and the need to develop effective clinical support mechanisms for standardized clinically actionable genetic information that can be shared across health systems.

Through research, we have been able to identify environmental exposures in IBD, but we need to improve integrating it into patient profiles. Planned investigations with multinational studies in the field of both basic laboratory science and epidemiological studies will help create extensive patient profiling that can be used in understanding disease processes and further patient care[28]. According to Valles-Colomer *et al*[57], the use of microbiology (metaomics) has allowed the analysis of bacteria present in people with IBD. In normal flora, the use of 16S rRNA sequencing identified Bacteroidetes and Firmicutes, interestingly in people with IBD, gastrointestinal biopsies have found decreased levels of these bacteria[57].

According to a study by Stankovic *et al*[58], the use of machine learning approaches by using artificial intelligence (AI) and algorithms creates patterns not seen before in the management of IBD[58]. By creating big datasets and then using linear regressions, logistic regressions, and fitting models to characterize risk factors, patient baseline characteristics, treatment plans, and prognosis can be predefined. To date, the largest database available for IBD is the IBD genomic database, which allowed the discovery of more than 200 IBD-related loci[57].

**Precision Medicine to predict treatment response and Prognosis**

The ability to predict if a treatment will fail is important as well, as it allows for early switching of therapy and improves the chances and cost-effectiveness of recapturing a positive response. The Personalized Anti-tumor necrosis factor (TNF) Therapy in CD Study (PANTS) followed 1610 patients on anti-TNF therapy for 12 mo or until therapy was withdrawn. The presence of low drug concentrations at week 14 demonstrated a connection to both primary nonresponse and the absence of remission at week 54. Patients on infliximab were more likely to have immunogenicity than those on adalimumab (62.8% *vs* 28.5%). Obesity at baseline was linked to nonremission at week 54 for adalimumab only, while smoking and immunomodulator use affected infliximab. HLA variants and glycosylation also affected anti-TNF therapy immunogenicity. Colonic biopsies obtained from patients diagnosed with UC revealed reduced levels of branched N-glycans, which served as an indicator of the inability to respond effectively to standard therapy. High levels of CRP were identified as the sole additional independent predictor in this context[59]. Single-cell gene expression technologies have been used to gain insights into the molecular mechanisms underlying drug response to comprehend the pathophysiology of this process. In cases of active UC, there is a distinct decrease in the expression of mitochondrial genes in the epithelial cells. Conversely, an exclusive cellular module in CD is observed in inflamed tissues, which is linked to the inability to achieve long-lasting remission with corticosteroids and anti-TNF therapy[4]. Not surprisingly, one study by Mishra *et al*[60], which analyzed the early shifts of gene expression and DNA methylation, found that patients resistant to TNF treatment lacked such signatures[60].

Single-cell profiling techniques can help identify and measure different cell populations and their transformations over time and location. Changes in cell behavior can disrupt the balance in IBD, and studying these changes using techniques like single-cell RNA-seq and ATAC-seq can help understand the complex spectrum of cell types that contribute to IBD pathogenesis[50]. In 2021, researchers developed yeast-based probiotics for the treatment of IBD. The engineered probiotics expressed a human P2Y2 purinergic receptor that senses extracellular ATP, a molecule involved in intestinal inflammation. Activation of the receptor led to the secretion of the ATP-degrading enzyme apyrase, which created a self-feedback mechanism to maintain extracellular ATP at normal levels. The engineered probiotics did not cause unwanted adverse effects such as inflammation-driven fibrosis or gut microbiota dysbiosis. This shows promise for the development of new therapies for IBD based on precision medicine approaches that target the gut microbiota[5,50].

Multiomics projects are currently underway to investigate the heterogeneity of IBD and improve precision management. However, these high-throughput data require advanced computational techniques, such as machine learning to model and analyze them. Machine learning includes supervised and unsupervised algorithms that could be used for patient clustering, predictions, and to detect novel biomarkers. These strategies have been successfully applied to integrated multiomics data in cancer therapy[2]. Incorporating the increasing array of biomarkers, prediction tools, and treatments into the field of IBD presents a notable difficulty. The combination of early intervention and these novel tools may provide the greatest opportunity for delivering precision medicine in IBD. Additionally, powerful tools and equipment are required to store and share a vast amount of data. The use of mobile phones and app technology is one of the significant advances in this field for collecting and sharing big data. However, knowledge and expertise are necessary to standardize the collection of data and translate the archived data into clinical applications. It is our responsibility to contribute to big data in IBD and practice high-quality biomarker-driven care to enable the provision of truly individualized patient care in the future[4,54,55].

Molecular profiling is another technique that can provide information on the genes involved in IBD. It is based on tissue and blood and can predict specific patterns. For example, one study showed which patients were responders *versus* nonresponders to anti-TNF induction using single transcripts such as the OSM, OSMR or TREM[61]. A study also differentiated responders *versus* nonresponders to vedolizumab based on the expression of *RGS13, DCHS2, MAATS1* and *P1Wil1*[56]. The PROFILE trial marks a groundbreaking advancement in medical research, being the inaugural prospective randomized control trial that used T-cell signatures to categorize patients at the time of diagnosis[62].

Deep learning models using convolutional neural networks, computer image analysis systems, and machine learning can predict disease severity and remission comparable to that of gastroenterologists and radiologists[63-65].

Waljee *et al*[66] used machine learning to predict steroid use and the risk of hospital admission in IBD patients. Developing such models can help in the therapeutic management of IBD patients[66]. Lee *et al*[67] describes 170 disease susceptibility loci in IBD and found that loci associated with the risk of developing IBD were not predictive of disease prognosis. This emphasizes the need to reassess GWASs based on patient phenotypes, response to treatment, and prognosis[67].

Finally, treatment with biologics can alter the transcriptome profiles of CD patients distinguishing naïve from exposed patients undergoing ileocolic resection. This knowledge can be used by clinicians in medical therapy decision-making postoperatively in adjunct to clinical factors and endoscopy[68].

Integrative approaches combining multiple omics to create a framework that assesses the complex factors that interplay in IBD are required. This should be established from the initial risk assessment, prevention of disease, disease categorization, subcategorization, treatment during the changing disease course, prognostication, and follow-up.

**Multiomics**

In recent decades, advances in technology have enabled the comprehensive profiling of the human gut microbiome through metaomics methodologies. The power of functional metaomics lies in its potential to identify molecular biomarkers that can assist with noninvasive screening and diagnosis, and treatment response. Data integration is the process of combining multiomics data[69,70]. Table 1 describes studies consulting using multiple layers of multiomics data. Recent comprehensive human omics studies have substantiated findings from murine models and enhanced our comprehension of the connections between bile acids, their microbial progenitors, intestinal inflammation, and tumorigenesis. However, a significant portion of these human omics studies predominantly focus on either metagenomics or bile-acid-related metabolomics rather than combining this data to elucidate the associations between fluctuations in the abundance or function of gut microbiota and bile acid concentrations[71]. There is an essential need for additional investigations to delineate the role of bile acids in the adaptive immune system, thereby facilitating the evolution of therapeutic agents and diagnostic tools for IDB and colorectal cancer (CRC). Targeting the gut microbiota–bile acid axis offers significant potential for CRC and IBD treatment and prognosis but requires extensive research to deepen our understanding of the mechanistic links and clinical implications[71].

The intestinal microbiota is increasingly viewed as a potentially influential factor in the onset of IBD and CRC. IBD and its association with CRC suggest a potentially shared etiology between these two conditions. It is suggested that genetic, environmental, and immunological factors play a role in the onset of these diseases; however, the mechanisms through which they exert their influence remain complex and ambiguous. Additionally, functional metaomics has revealed similar metabolic dysregulation in both IBD and CRC, suggesting a disruption in host–microbiota interaction leading to abnormal immune responses and inflammation[72].

In another study, omics data were utilized to profile prospective patients undergoing either anticytokine or anti-integrin therapy. Certain bacterial species linked to a decrease in inflammation, often by creating a beneficial fecal short-chain fatty acid profile, were associated with patients more likely to achieve remission with anticytokine therapy. Moreover, these patients had an increased presence of colonic-butyrate-producing species that promoted intestinal balance. Those undergoing anti-integrin therapy who successfully achieved remission demonstrated increased abundances of different bacterial species, such as *Bifidobacterium longum* and *Bacteroides* species. Interestingly, some of these bacteria have previously shown effectiveness in independent microbiome-based therapies. However, the correlation between the microbiome and clinical response was more significant in week 14 of remission than in week 52 outcomes, suggesting the microbiome’s influence may be on early response[73]. In this study, it was demonstrated that metabolomic profiling also contributed to understanding patient responses to treatment, with a strong association found between serum secondary bile acid concentrations and the likelihood of achieving remission with anti-cytokine therapy[74].

The Integrated Bowel Disease Microbiome Database study, part of the Human Microbiome Project Phase 2, investigated the gut microbiome of IBD. They used various measurement methods to analyze the microbiome's molecular components in CD and UC. The study found unique molecular features associated with dysbiosis in IBD, including previously known and new findings. The stability of the microbiome varied across IBD phenotypes and disease activity. The study identified potential targets for further investigation and highlighted the need to translate the findings into clinical applications, such as predictive biomarkers and new treatments for IBD[75].

The Danish IBD biobank project on 840 patients naïve to biologics started on biological therapy. It is an ongoing 3-year study utilizing clinical patient data, transcriptomic, proteomic, and microbiomic data. The study aims to identify biomarkers for response to biological therapy and understanding disease courses in IBD patients. The IBD prognosis study, 1000 IBD project, Swedish IBD quality register, and the Dutch IBD biobank are similar multi-omics integration studies and datasets for IBD[52,76,77].

The expansion of advanced platforms and tools for omics analysis signifies a change in molecular epidemiological research. Although the current omics data of IBD development is limited, the field is rapidly growing and presents immense possibilities. Various human cohorts, including those involving diverse births, at-risk individuals, and prediagnostic stages, have been established. Ongoing multiomics studies aim to characterize the pathways associated with IBD, incorporating the use of novel biomarkers. Rigorous statistical analyses, long-term monitoring of omics patterns in individuals before and after the onset of IBD, and replication of findings in independent cohorts are expected to provide valuable insights. To draw reliable conclusions from individual studies and facilitate the integration of data from multiple studies, it is crucial to collect detailed clinical information and follow standardized sampling, storage, and analysis protocols.

Availability of the knowledge acquired from precision medicine across all socioeconomic statuses is essential. Current data on precision medicine is not diverse and is restricted to some groups of populations. In a systematic review by Norris *et al*[78], those with low socioeconomic status were 17% less likely to be treated with novel precision medicine therapies for cancer[78]. Spratt *et al*[79] describes in his study of 5729 genomic sequencing samples that only 12% were African American and 3% were Hispanic and 3% were Asian. This over-represents the white population and under-represents other communities[79]. The results of such research can have an impact on the understanding of disease pathogenesis and the generalizability of results globally[80]. In a study by Yeh *et al*[81], African Americans and Hispanics questioned the benefits of precision medicine to their population due to the current inequalities in health care access and quality[81]. Another example of such a difference was seen by Lynch *et al*[82] in their study on Medicare patients with lung cancer. The authors observed racial, income, and regional disparities in EGFR testing and underutilization of guideline-recommended testing in certain populations. Precision medicine is advancing in terms of the complexity of disease management. The benefits of precision medicine need to be available to everyone equally, and a conscious effort to not increase the existing gap in health care is necessary[82].

Advancements in analysis techniques of omics data hold the potential to revolutionize the molecular epidemiology of IBD and other diseases, especially as more high-quality studies are conducted. This could lead to improved prediction of IBD onset and the development of treatment and preventive strategies. Furthermore, the findings in such studies can serve as a foundation to unravel pathways relevant to other immune-mediated and chronic diseases, contributing to advancements in public health as a whole[65].

**Future directions**

With the upcoming evolution of AI to develop algorithms to diagnose and treat diseases, using databases will be the pillar of collecting information and analyzing trends with the help of statistical systems. It is essential to combine these individual databases so that by documenting known patient factors, specific profiles that will allow us to treat patients with specific patterns are generated. The complexity and heterogeneity of IBD make it a challenge because it is an evolving disease, and one treatment will not fit all patients. The future of IBD relies on these multiomics databases and the integration of profiles targeting different omics layers.

Establishing a checklist for future studies on precision medicine in IBD to regulate the methodology, quality, model validation, external validation, and algorithmic bias. Utilizing checklists to ensure reproducibility from study conduction to analysis and study data presentation will allow a better understanding of study outcomes and allow its applicability globally.

Efforts to minimize the current socioeconomic and racial gap in health care and precision medicine by ensuring further research include minority groups in diagnostics, drug discovery, and disease management.

Information about barriers to participation based on sex, race, and socioeconomic status is essential to help in the recruitment of underrepresented samples and ensure results are generalizable.

Precision medicine is promising, but the cost of genomic sequencing and creating patient profiles is not affordable to all patients. This could lead to further disparities in health care and is a barrier to its widespread adoption.

Large complex data needs to be standardized and integrated to achieve the full benefit of precision medicine. Establishing standards for collecting widely variable genomic data to allow comparison across studies is necessary.

Another important concept is the ethical aspects of utilizing genetic and patient data, ensuring patient privacy, and preventing data misuse.

There is a wide gap from creation to translation of the extensive research that is being generated on omics data. The complex information generated needs to be integrated and translated to patient care. This process involves rigorous clinical evidence, standardization, cost-benefit assessment, and regulations.

***Summary of key points***

Defining and understanding IBD requires a multidisciplinary approach by taking the genome, exposome, microbiome, immunome, proteome, transcriptome, epigenome, and metabolome concepts as a unit.

The development of GWASs has allowed the identification of notable genetic risk regions and IBD phenotypes. Other pathways have been developed, including microbial sensing, the maintenance of intestinal barrier function, signaling within the innate and adaptive immune system, fibrosis development, and cellular homeostasis.

Regarding the environmental risk factors, databases like the United Kingdom Biobank have allowed the recognition of polygenic risk factors like smoking, childhood antibiotic use, sun exposure in the winter, socioeconomic factors, and oral contraceptive use to be related to IBD occurrence.

The study of proteins has always been a target for diagnosis and treatment. One example is the TL1A, which has been involved in colonic inflammation and fibrosis through epithelial-to-mesenchymal cell transition and immune response mechanisms.

The interaction of our gut with the microorganisms that form part of the habitat in our intestine has also been the target of studies like the CERTIFIED study, where patients treated with ustekinumab, bacteria like *Faecalibacterium* and *Bacteroides* were found in baseline stool in CD patients who achieved remission.

The use of databases and AI creates the possibility of algorithms not seen before for the treatment and management of IBD, with the use of linear, logistic regressions and fitting models to characterize risk factors, baseline characteristics, treatment plans, and prognosis.

**CONCLUSION**

IBD is a complex longitudinal disease that utilizes multiple omics such as genomics, epigenomics, microbiomics, proteomics and immunomics. Utilizing mutiomics to further IBD management and deliver precision medicine with next-level care in IBD patients for the current and future should be targeted.

**REFERENCES**

1 **Definition of precision medicine**. NCI Dictionary of Cancer Terms-NCI. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/precision-medicine

2 **Liu XY**, Tang H, Zhou QY, Zeng YL, Chen D, Xu H, Li Y, Tan B, Qian JM. Advancing the precision management of inflammatory bowel disease in the era of omics approaches and new technology. *World J Gastroenterol* 2023; **29**: 272-285 [PMID: 36687128 DOI: 10.3748/wjg.v29.i2.272]

3 **Thomas JP**, Modos D, Korcsmaros T, Brooks-Warburton J. Network Biology Approaches to Achieve Precision Medicine in Inflammatory Bowel Disease. *Front Genet* 2021; **12**: 760501 [PMID: 34745229 DOI: 10.3389/fgene.2021.760501]

4 **Borg-Bartolo SP**, Boyapati RK, Satsangi J, Kalla R. Precision medicine in inflammatory bowel disease: concept, progress and challenges. *F1000Res* 2020; **9** [PMID: 32047622 DOI: 10.12688/f1000research.20928.1]

5 **Denson LA**, Curran M, McGovern DPB, Koltun WA, Duerr RH, Kim SC, Sartor RB, Sylvester FA, Abraham C, de Zoeten EF, Siegel CA, Burns RM, Dobes AM, Shtraizent N, Honig G, Heller CA, Hurtado-Lorenzo A, Cho JH. Challenges in IBD Research: Precision Medicine. *Inflamm Bowel Dis* 2019; **25**: S31-S39 [PMID: 31095701 DOI: 10.1093/ibd/izz078]

6 **Cleynen I**, Boucher G, Jostins L, Schumm LP, Zeissig S, Ahmad T, Andersen V, Andrews JM, Annese V, Brand S, Brant SR, Cho JH, Daly MJ, Dubinsky M, Duerr RH, Ferguson LR, Franke A, Gearry RB, Goyette P, Hakonarson H, Halfvarson J, Hov JR, Huang H, Kennedy NA, Kupcinskas L, Lawrance IC, Lee JC, Satsangi J, Schreiber S, Théâtre E, van der Meulen-de Jong AE, Weersma RK, Wilson DC; International Inflammatory Bowel Disease Genetics Consortium, Parkes M, Vermeire S, Rioux JD, Mansfield J, Silverberg MS, Radford-Smith G, McGovern DP, Barrett JC, Lees CW. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. *Lancet* 2016; **387**: 156-167 [PMID: 26490195 DOI: 10.1016/S0140-6736(15)00465-1]

7 **Graham DB**, Xavier RJ. Pathway paradigms revealed from the genetics of inflammatory bowel disease. *Nature* 2020; **578**: 527-539 [PMID: 32103191 DOI: 10.1038/s41586-020-2025-2]

8 **Ellinghaus D**, Jostins L, Spain SL, Cortes A, Bethune J, Han B, Park YR, Raychaudhuri S, Pouget JG, Hübenthal M, Folseraas T, Wang Y, Esko T, Metspalu A, Westra HJ, Franke L, Pers TH, Weersma RK, Collij V, D'Amato M, Halfvarson J, Jensen AB, Lieb W, Degenhardt F, Forstner AJ, Hofmann A; International IBD Genetics Consortium (IIBDGC); International Genetics of Ankylosing Spondylitis Consortium (IGAS); International PSC Study Group (IPSCSG); Genetic Analysis of Psoriasis Consortium (GAPC); Psoriasis Association Genetics Extension (PAGE), Schreiber S, Mrowietz U, Juran BD, Lazaridis KN, Brunak S, Dale AM, Trembath RC, Weidinger S, Weichenthal M, Ellinghaus E, Elder JT, Barker JN, Andreassen OA, McGovern DP, Karlsen TH, Barrett JC, Parkes M, Brown MA, Franke A. Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. *Nat Genet* 2016; **48**: 510-518 [PMID: 26974007 DOI: 10.1038/ng.3528]

9 **Girardin SE**, Hugot JP, Sansonetti PJ. Lessons from Nod2 studies: towards a link between Crohn's disease and bacterial sensing. *Trends Immunol* 2003; **24**: 652-658 [PMID: 14644139 DOI: 10.1016/j.it.2003.10.007]

10 **Ashton JJ**, Mossotto E, Ennis S, Beattie RM. Personalising medicine in inflammatory bowel disease-current and future perspectives. *Transl Pediatr* 2019; **8**: 56-69 [PMID: 30881899 DOI: 10.21037/tp.2018.12.03]

11 **Latiano A**, Palmieri O, Cucchiara S, Castro M, D'Incà R, Guariso G, Dallapiccola B, Valvano MR, Latiano T, Andriulli A, Annese V. Polymorphism of the IRGM gene might predispose to fistulizing behavior in Crohn's disease. *Am J Gastroenterol* 2009; **104**: 110-116 [PMID: 19098858 DOI: 10.1038/ajg.2008.3]

12 **Deepak P**, Sandborn WJ. Ustekinumab and Anti-Interleukin-23 Agents in Crohn's Disease. *Gastroenterol Clin North Am* 2017; **46**: 603-626 [PMID: 28838418 DOI: 10.1016/j.gtc.2017.05.013]

13 **Meena S**, Varla H, Swaminathan VV, Chandar R, Jayakumar I, Ramakrishnan B, Uppuluri R, Raj R. Hematopoietic stem cell Transplantation in Children with very Early Onset Inflammatory Bowel Disease Secondary to Monogenic Disorders of immune-dysregulation. *Indian J Hematol Blood Transfus* 2023; **39**: 183-190 [PMID: 37006985 DOI: 10.1007/s12288-022-01586-2]

14 **Moser LM**, Fekadu J, Willasch A, Rettinger E, Sörensen J, Jarisch A, Kirwil M, Lieb A, Holzinger D, Calaminus G, Bader P, Bakhtiar S. Treatment of inborn errors of immunity patients with inflammatory bowel disease phenotype by allogeneic stem cell transplantation. *Br J Haematol* 2023; **200**: 595-607 [PMID: 36214981 DOI: 10.1111/bjh.18497]

15 **Lightner AL**, Dadgar N, Matyas C, Elliott K, Fulmer C, Khaitan N, Ream J, Nachand D, Steele SR. A phase IB/IIA study of remestemcel-L, an allogeneic bone marrow-derived mesenchymal stem cell product, for the treatment of medically refractory ulcerative colitis: an interim analysis. *Colorectal Dis* 2022; **24**: 1358-1370 [PMID: 35767384 DOI: 10.1111/codi.16239]

16 **Ye Z**, Zhou Y, Huang Y, Wang Y, Lu J, Tang Z, Miao S, Dong K, Jiang Z. Phenotype and Management of Infantile-onset Inflammatory Bowel Disease: Experience from a Tertiary Care Center in China. *Inflamm Bowel Dis* 2017; **23**: 2154-2164 [PMID: 29140941 DOI: 10.1097/MIB.0000000000001269]

17 **Engelhardt KR**, Shah N, Faizura-Yeop I, Kocacik Uygun DF, Frede N, Muise AM, Shteyer E, Filiz S, Chee R, Elawad M, Hartmann B, Arkwright PD, Dvorak C, Klein C, Puck JM, Grimbacher B, Glocker EO. Clinical outcome in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2013; **131**: 825-830 [PMID: 23158016 DOI: 10.1016/j.jaci.2012.09.025]

18 **Ono S**, Takeshita K, Kiridoshi Y, Kato M, Kamiya T, Hoshino A, Yanagimachi M, Arai K, Takeuchi I, Toita N, Imamura T, Sasahara Y, Sugita J, Hamamoto K, Takeuchi M, Saito S, Onuma M, Tsujimoto H, Yasui M, Taga T, Arakawa Y, Mitani Y, Yamamoto N, Imai K, Suda W, Hattori M, Ohara O, Morio T, Honda K, Kanegane H. Hematopoietic Cell Transplantation Rescues Inflammatory Bowel Disease and Dysbiosis of Gut Microbiota in XIAP Deficiency. *J Allergy Clin Immunol Pract* 2021; **9**: 3767-3780 [PMID: 34246792 DOI: 10.1016/j.jaip.2021.05.045]

19 **Fujikawa H**, Shimizu H, Nambu R, Takeuchi I, Matsui T, Sakamoto K, Gocho Y, Miyamoto T, Yasumi T, Yoshioka T, Arai K. Monogenic inflammatory bowel disease with STXBP2 mutations is not resolved by hematopoietic stem cell transplantation but can be alleviated *via* immunosuppressive drug therapy. *Clin Immunol* 2023; **246**: 109203 [PMID: 36503158 DOI: 10.1016/j.clim.2022.109203]

20 **Kammermeier J**, Drury S, James CT, Dziubak R, Ocaka L, Elawad M, Beales P, Lench N, Uhlig HH, Bacchelli C, Shah N. Targeted gene panel sequencing in children with very early onset inflammatory bowel disease--evaluation and prospective analysis. *J Med Genet* 2014; **51**: 748-755 [PMID: 25194001 DOI: 10.1136/jmedgenet-2014-102624]

21 **Kammermeier J**, Lamb CA, Jones KDJ, Anderson CA, Baple EL, Bolton C, Braggins H, Coulter TI, Gilmour KC, Gregory V, Hambleton S, Hartley D, Hawthorne AB, Hearn S, Laurence A, Parkes M, Russell RK, Speight RA, Travis S, Wilson DC, Uhlig HH. Genomic diagnosis and care co-ordination for monogenic inflammatory bowel disease in children and adults: consensus guideline on behalf of the British Society of Gastroenterology and British Society of Paediatric Gastroenterology, Hepatology and Nutrition. *Lancet Gastroenterol Hepatol* 2023; **8**: 271-286 [PMID: 36634696 DOI: 10.1016/S2468-1253(22)00337-5]

22 **Dominguez-Salas P**, Moore SE, Baker MS, Bergen AW, Cox SE, Dyer RA, Fulford AJ, Guan Y, Laritsky E, Silver MJ, Swan GE, Zeisel SH, Innis SM, Waterland RA, Prentice AM, Hennig BJ. Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. *Nat Commun* 2014; **5**: 3746 [PMID: 24781383 DOI: 10.1038/ncomms4746]

23 **Fernandez-Twinn DS**, Constância M, Ozanne SE. Intergenerational epigenetic inheritance in models of developmental programming of adult disease. *Semin Cell Dev Biol* 2015; **43**: 85-95 [PMID: 26135290 DOI: 10.1016/j.semcdb.2015.06.006]

24 **Pan WH**, Sommer F, Falk-Paulsen M, Ulas T, Best P, Fazio A, Kachroo P, Luzius A, Jentzsch M, Rehman A, Müller F, Lengauer T, Walter J, Künzel S, Baines JF, Schreiber S, Franke A, Schultze JL, Bäckhed F, Rosenstiel P. Exposure to the gut microbiota drives distinct methylome and transcriptome changes in intestinal epithelial cells during postnatal development. *Genome Med* 2018; **10**: 27 [PMID: 29653584 DOI: 10.1186/s13073-018-0534-5]

25 **Sun Y**, Yuan S, Chen X, Sun J, Kalla R, Yu L, Wang L, Zhou X, Kong X, Hesketh T, Ho GT, Ding K, Dunlop M, Larsson SC, Satsangi J, Chen J, Wang X, Li X, Theodoratou E, Giovannucci EL. The Contribution of Genetic Risk and Lifestyle Factors in the Development of Adult-Onset Inflammatory Bowel Disease: A Prospective Cohort Study. *Am J Gastroenterol* 2023; **118**: 511-522 [PMID: 36695739 DOI: 10.14309/ajg.0000000000002180]

26 **Yang AZ**, Jostins-Dean L. Environmental variables and genome-environment interactions predicting IBD diagnosis in large UK cohort. *Sci Rep* 2022; **12**: 10890 [PMID: 35764673 DOI: 10.1038/s41598-022-13222-0]

27 **Ryan FJ**, Ahern AM, Fitzgerald RS, Laserna-Mendieta EJ, Power EM, Clooney AG, O'Donoghue KW, McMurdie PJ, Iwai S, Crits-Christoph A, Sheehan D, Moran C, Flemer B, Zomer AL, Fanning A, O'Callaghan J, Walton J, Temko A, Stack W, Jackson L, Joyce SA, Melgar S, DeSantis TZ, Bell JT, Shanahan F, Claesson MJ. Colonic microbiota is associated with inflammation and host epigenomic alterations in inflammatory bowel disease. *Nat Commun* 2020; **11**: 1512 [PMID: 32251296 DOI: 10.1038/s41467-020-15342-5]

28 **Noble CL**, Abbas AR, Lees CW, Cornelius J, Toy K, Modrusan Z, Clark HF, Arnott ID, Penman ID, Satsangi J, Diehl L. Characterization of intestinal gene expression profiles in Crohn's disease by genome-wide microarray analysis. *Inflamm Bowel Dis* 2010; **16**: 1717-1728 [PMID: 20848455 DOI: 10.1002/ibd.21263]

29 **van der Sloot KWJ**, Weersma RK, Alizadeh BZ, Dijkstra G. Identification of Environmental Risk Factors Associated With the Development of Inflammatory Bowel Disease. *J Crohns Colitis* 2020; **14**: 1662-1671 [PMID: 32572465 DOI: 10.1093/ecco-jcc/jjaa114]

30 **Rogler G**, Vavricka S. Exposome in IBD: recent insights in environmental factors that influence the onset and course of IBD. *Inflamm Bowel Dis* 2015; **21**: 400-408 [PMID: 25358064 DOI: 10.1097/MIB.0000000000000229]

31 **Vieujean S**, Caron B, Haghnejad V, Jouzeau JY, Netter P, Heba AC, Ndiaye NC, Moulin D, Barreto G, Danese S, Peyrin-Biroulet L. Impact of the Exposome on the Epigenome in Inflammatory Bowel Disease Patients and Animal Models. *Int J Mol Sci* 2022; **23** [PMID: 35886959 DOI: 10.3390/ijms23147611]

32 **Lamb CA**, Saifuddin A, Powell N, Rieder F. The Future of Precision Medicine to Predict Outcomes and Control Tissue Remodeling in Inflammatory Bowel Disease. *Gastroenterology* 2022; **162**: 1525-1542 [PMID: 34995532 DOI: 10.1053/j.gastro.2021.09.077]

33 **Svolos V**, Hansen R, Nichols B, Quince C, Ijaz UZ, Papadopoulou RT, Edwards CA, Watson D, Alghamdi A, Brejnrod A, Ansalone C, Duncan H, Gervais L, Tayler R, Salmond J, Bolognini D, Klopfleisch R, Gaya DR, Milling S, Russell RK, Gerasimidis K. Treatment of Active Crohn's Disease With an Ordinary Food-based Diet That Replicates Exclusive Enteral Nutrition. *Gastroenterology* 2019; **156**: 1354-1367.e6 [PMID: 30550821 DOI: 10.1053/j.gastro.2018.12.002]

34 **To N**, Gracie DJ, Ford AC. Systematic review with meta-analysis: the adverse effects of tobacco smoking on the natural history of Crohn's disease. *Aliment Pharmacol Ther* 2016; **43**: 549-561 [PMID: 26749371 DOI: 10.1111/apt.13511]

35 **Yau YY**, Leong RWL, Pudipeddi A, Redmond D, Wasinger VC. Serological Epithelial Component Proteins Identify Intestinal Complications in Crohn's Disease. *Mol Cell Proteomics* 2017; **16**: 1244-1257 [PMID: 28490445 DOI: 10.1074/mcp.M116.066506]

36 **Deeke SA**, Starr AE, Ning Z, Ahmadi S, Zhang X, Mayne J, Chiang CK, Singleton R, Benchimol EI, Mack DR, Stintzi A, Figeys D. Mucosal-luminal interface proteomics reveals biomarkers of pediatric inflammatory bowel disease-associated colitis. *Am J Gastroenterol* 2018; **113**: 713-724 [PMID: 29531307 DOI: 10.1038/s41395-018-0024-9]

37 **Seeley EH**, Washington MK, Caprioli RM, M'Koma AE. Proteomic patterns of colonic mucosal tissues delineate Crohn's colitis and ulcerative colitis. *Proteomics Clin Appl* 2013; **7**: 541-549 [PMID: 23382084 DOI: 10.1002/prca.201200107]

38 **M'Koma AE**, Seeley EH, Washington MK, Schwartz DA, Muldoon RL, Herline AJ, Wise PE, Caprioli RM. Proteomic profiling of mucosal and submucosal colonic tissues yields protein signatures that differentiate the inflammatory colitides. *Inflamm Bowel Dis* 2011; **17**: 875-883 [PMID: 20806340 DOI: 10.1002/ibd.21442]

39 **Starr AE**, Deeke SA, Ning Z, Chiang CK, Zhang X, Mottawea W, Singleton R, Benchimol EI, Wen M, Mack DR, Stintzi A, Figeys D. Proteomic analysis of ascending colon biopsies from a paediatric inflammatory bowel disease inception cohort identifies protein biomarkers that differentiate Crohn's disease from UC. *Gut* 2017; **66**: 1573-1583 [PMID: 27216938 DOI: 10.1136/gutjnl-2015-310705]

40 **Magnusson MK**, Strid H, Isaksson S, Bajor A, Lasson A, Ung KA, Öhman L. Response to infliximab therapy in ulcerative colitis is associated with decreased monocyte activation, reduced CCL2 expression and downregulation of Tenascin C. *J Crohns Colitis* 2015; **9**: 56-65 [PMID: 25518051 DOI: 10.1093/ecco-jcc/jju008]

41 **De Vos M**, Dewit O, D'Haens G, Baert F, Fontaine F, Vermeire S, Franchimont D, Moreels T, Staessen D, Terriere L, Vander Cruyssen B, Louis E; behalf of BIRD. Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNF naïve patients with ulcerative colitis. *J Crohns Colitis* 2012; **6**: 557-562 [PMID: 22398050 DOI: 10.1016/j.crohns.2011.11.002]

42 **Facciorusso A**, Ramai D, Ricciardelli C, Paolillo R, Maida M, Chandan S, Mohan BP, Domislovic V, Sacco R. Prognostic Role of Post-Induction Fecal Calprotectin Levels in Patients with Inflammatory Bowel Disease Treated with Biological Therapies. *Biomedicines* 2022; **10** [PMID: 36140408 DOI: 10.3390/biomedicines10092305]

43 **Wenxiu J**, Mingyue Y, Fei H, Yuxin L, Mengyao W, Chenyang L, Jia S, Hong Z, Shih DQ, Targan SR, Xiaolan Z. Effect and Mechanism of TL1A Expression on Epithelial-Mesenchymal Transition during Chronic Colitis-Related Intestinal Fibrosis. *Mediators Inflamm* 2021; **2021**: 5927064 [PMID: 34257516 DOI: 10.1155/2021/5927064]

44 **Masoodi M**, Pearl DS, Eiden M, Shute JK, Brown JF, Calder PC, Trebble TM. Altered colonic mucosal Polyunsaturated Fatty Acid (PUFA) derived lipid mediators in ulcerative colitis: new insight into relationship with disease activity and pathophysiology. *PLoS One* 2013; **8**: e76532 [PMID: 24204637 DOI: 10.1371/journal.pone.0076532]

45 **Titz B**, Gadaleta RM, Lo Sasso G, Elamin A, Ekroos K, Ivanov NV, Peitsch MC, Hoeng J. Proteomics and Lipidomics in Inflammatory Bowel Disease Research: From Mechanistic Insights to Biomarker Identification. *Int J Mol Sci* 2018; **19** [PMID: 30223557 DOI: 10.3390/ijms19092775]

46 **Bennike TB**, Carlsen TG, Ellingsen T, Bonderup OK, Glerup H, Bøgsted M, Christiansen G, Birkelund S, Stensballe A, Andersen V. Neutrophil Extracellular Traps in Ulcerative Colitis: A Proteome Analysis of Intestinal Biopsies. *Inflamm Bowel Dis* 2015; **21**: 2052-2067 [PMID: 25993694 DOI: 10.1097/MIB.0000000000000460]

47 **Ananthakrishnan AN**, Luo C, Yajnik V, Khalili H, Garber JJ, Stevens BW, Cleland T, Xavier RJ. Gut Microbiome Function Predicts Response to Anti-integrin Biologic Therapy in Inflammatory Bowel Diseases. *Cell Host Microbe* 2017; **21**: 603-610.e3 [PMID: 28494241 DOI: 10.1016/j.chom.2017.04.010]

48 **Gevers D**, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, Schwager E, Knights D, Song SJ, Yassour M, Morgan XC, Kostic AD, Luo C, González A, McDonald D, Haberman Y, Walters T, Baker S, Rosh J, Stephens M, Heyman M, Markowitz J, Baldassano R, Griffiths A, Sylvester F, Mack D, Kim S, Crandall W, Hyams J, Huttenhower C, Knight R, Xavier RJ. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe* 2014; **15**: 382-392 [PMID: 24629344 DOI: 10.1016/j.chom.2014.02.005]

49 **Vázquez-Baeza Y**, Callewaert C, Debelius J, Hyde E, Marotz C, Morton JT, Swafford A, Vrbanac A, Dorrestein PC, Knight R. Impacts of the Human Gut Microbiome on Therapeutics. *Annu Rev Pharmacol Toxicol* 2018; **58**: 253-270 [PMID: 28968189 DOI: 10.1146/annurev-pharmtox-042017-031849]

50 **Mao R**, Chen M. Precision medicine in IBD: genes, drugs, bugs and omics. *Nat Rev Gastroenterol Hepatol* 2022; **19**: 81-82 [PMID: 34785787 DOI: 10.1038/s41575-021-00555-w]

51 **Dovrolis N**, Filidou E, Kolios G. Systems biology in inflammatory bowel diseases: on the way to precision medicine. *Ann Gastroenterol* 2019; **32**: 233-246 [PMID: 31040620 DOI: 10.20524/aog.2019.0373]

52 **Spekhorst LM**, Imhann F, Festen EAM, van Bodegraven AA, de Boer NKH, Bouma G, Fidder HH, d'Haens G, Hoentjen F, Hommes DW, de Jong DJ, Löwenberg M, Maljaars PWJ, van der Meulen-de Jong AE, Oldenburg B, Pierik MJ, Ponsioen CY, Stokkers PC, Verspaget HW, Visschedijk MC, van der Woude CJ, Dijkstra G, Weersma RK; Parelsnoer Institute (PSI) and the Dutch Initiative on Crohn and Colitis (ICC). Cohort profile: design and first results of the Dutch IBD Biobank: a prospective, nationwide biobank of patients with inflammatory bowel disease. *BMJ Open* 2017; **7**: e016695 [PMID: 29122790 DOI: 10.1136/bmjopen-2017-016695]

53 **Chaparro M**, Ramas M, Benítez JM, López-García A, Juan A, Guardiola J, Mínguez M, Calvet X, Márquez L, Fernández Salazar LI, Bujanda L, García C, Zabana Y, Lorente R, Barrio J, Hinojosa E, Iborra M, Cajal MD, Van Domselaar M, García-Sepulcre MF, Gomollón F, Piqueras M, Alcaín G, García-Sánchez V, Panés J, Domènech E, García-Esquinas E, Rodríguez-Artalejo F, Gisbert JP. Extracolonic Cancer in Inflammatory Bowel Disease: Data from the GETECCU Eneida Registry. *Am J Gastroenterol* 2017; **112**: 1135-1143 [PMID: 28534520 DOI: 10.1038/ajg.2017.96]

54 **Khodadadian A**, Darzi S, Haghi-Daredeh S, Sadat Eshaghi F, Babakhanzadeh E, Mirabutalebi SH, Nazari M. Genomics and Transcriptomics: The Powerful Technologies in Precision Medicine. *Int J Gen Med* 2020; **13**: 627-640 [PMID: 32982380 DOI: 10.2147/IJGM.S249970]

55 **Noor NM**, Sousa P, Paul S, Roblin X. Early Diagnosis, Early Stratification, and Early Intervention to Deliver Precision Medicine in IBD. *Inflamm Bowel Dis* 2022; **28**: 1254-1264 [PMID: 34480558 DOI: 10.1093/ibd/izab228]

56 **Verstockt B**, Verstockt S, Veny M, Dehairs J, Arnauts K, Van Assche G, De Hertogh G, Vermeire S, Salas A, Ferrante M. Expression Levels of 4 Genes in Colon Tissue Might Be Used to Predict Which Patients Will Enter Endoscopic Remission After Vedolizumab Therapy for Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol* 2020; **18**: 1142-1151.e10 [PMID: 31446181 DOI: 10.1016/j.cgh.2019.08.030]

57 **Valles-Colomer M**, Darzi Y, Vieira-Silva S, Falony G, Raes J, Joossens M. Meta-omics in Inflammatory Bowel Disease Research: Applications, Challenges, and Guidelines. *J Crohns Colitis* 2016; **10**: 735-746 [PMID: 26802086 DOI: 10.1093/ecco-jcc/jjw024]

58 **Stankovic B**, Kotur N, Nikcevic G, Gasic V, Zukic B, Pavlovic S. Machine Learning Modeling from Omics Data as Prospective Tool for Improvement of Inflammatory Bowel Disease Diagnosis and Clinical Classifications. *Genes (Basel)* 2021; **12** [PMID: 34573420 DOI: 10.3390/genes12091438]

59 **Kennedy NA**, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, Thomas A, Nice R, Perry MH, Bouri S, Chanchlani N, Heerasing NM, Hendy P, Lin S, Gaya DR, Cummings JRF, Selinger CP, Lees CW, Hart AL, Parkes M, Sebastian S, Mansfield JC, Irving PM, Lindsay J, Russell RK, McDonald TJ, McGovern D, Goodhand JR, Ahmad T; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019; **4**: 341-353 [PMID: 30824404 DOI: 10.1016/S2468-1253(19)30012-3]

60 **Mishra N**, Aden K, Blase JI, Baran N, Bordoni D, Tran F, Conrad C, Avalos D, Jaeckel C, Scherer M, Sørensen SB, Overgaard SH, Schulte B, Nikolaus S, Rey G, Gasparoni G, Lyons PA, Schultze JL, Walter J, Andersen V; SYSCID Consortium, Dermitzakis ET, Schreiber S, Rosenstiel P. Longitudinal multi-omics analysis identifies early blood-based predictors of anti-TNF therapy response in inflammatory bowel disease. *Genome Med* 2022; **14**: 110 [PMID: 36153599 DOI: 10.1186/s13073-022-01112-z]

61 **West NR**, Hegazy AN, Owens BMJ, Bullers SJ, Linggi B, Buonocore S, Coccia M, Görtz D, This S, Stockenhuber K, Pott J, Friedrich M, Ryzhakov G, Baribaud F, Brodmerkel C, Cieluch C, Rahman N, Müller-Newen G, Owens RJ, Kühl AA, Maloy KJ, Plevy SE; Oxford IBD Cohort Investigators, Keshav S, Travis SPL, Powrie F. Oncostatin M drives intestinal inflammation and predicts response to tumor necrosis factor-neutralizing therapy in patients with inflammatory bowel disease. *Nat Med* 2017; **23**: 579-589 [PMID: 28368383 DOI: 10.1038/nm.4307]

62 **Parkes M**, Noor NM, Dowling F, Leung H, Bond S, Whitehead L, Upponi S, Kinnon P, Sandham AP, Lyons PA, McKinney EF, Smith KGC, Lee JC. PRedicting Outcomes For Crohn's dIsease using a moLecular biomarkEr (PROFILE): protocol for a multicentre, randomised, biomarker-stratified trial. *BMJ Open* 2018; **8**: e026767 [PMID: 30523133 DOI: 10.1136/bmjopen-2018-026767]

63 **Stidham RW**, Liu W, Bishu S, Rice MD, Higgins PDR, Zhu J, Nallamothu BK, Waljee AK. Performance of a Deep Learning Model *vs* Human Reviewers in Grading Endoscopic Disease Severity of Patients With Ulcerative Colitis. *JAMA Netw Open* 2019; **2**: e193963 [PMID: 31099869 DOI: 10.1001/jamanetworkopen.2019.3963]

64 **Stidham RW**, Enchakalody B, Waljee AK, Higgins PDR, Wang SC, Su GL, Wasnik AP, Al-Hawary M. Assessing Small Bowel Stricturing and Morphology in Crohn's Disease Using Semi-automated Image Analysis. *Inflamm Bowel Dis* 2020; **26**: 734-742 [PMID: 31504540 DOI: 10.1093/ibd/izz196]

65 **Reddy BK**, Delen D, Agrawal RK. Predicting and explaining inflammation in Crohn's disease patients using predictive analytics methods and electronic medical record data. *Health Informatics J* 2019; **25**: 1201-1218 [PMID: 29320910 DOI: 10.1177/1460458217751015]

66 **Waljee AK**, Lipson R, Wiitala WL, Zhang Y, Liu B, Zhu J, Wallace B, Govani SM, Stidham RW, Hayward R, Higgins PDR. Predicting Hospitalization and Outpatient Corticosteroid Use in Inflammatory Bowel Disease Patients Using Machine Learning. *Inflamm Bowel Dis* 2017; **24**: 45-53 [PMID: 29272474 DOI: 10.1093/ibd/izx007]

67 **Lee JC**, Biasci D, Roberts R, Gearry RB, Mansfield JC, Ahmad T, Prescott NJ, Satsangi J, Wilson DC, Jostins L, Anderson CA; UK IBD Genetics Consortium, Traherne JA, Lyons PA, Parkes M, Smith KG. Genome-wide association study identifies distinct genetic contributions to prognosis and susceptibility in Crohn's disease. *Nat Genet* 2017; **49**: 262-268 [PMID: 28067912 DOI: 10.1038/ng.3755]

68 **Cushing KC**, Mclean R, McDonald KG, Gustafsson JK, Knoop KA, Kulkarni DH, Sartor RB, Newberry RD. Predicting Risk of Postoperative Disease Recurrence in Crohn's Disease: Patients With Indolent Crohn's Disease Have Distinct Whole Transcriptome Profiles at the Time of First Surgery. *Inflamm Bowel Dis* 2019; **25**: 180-193 [PMID: 29982468 DOI: 10.1093/ibd/izy228]

69 **Gligorijević V**, Pržulj N. Methods for biological data integration: perspectives and challenges. *J R Soc Interface* 2015; **12** [PMID: 26490630 DOI: 10.1098/rsif.2015.0571]

70 **Argelaguet R**, Velten B, Arnol D, Dietrich S, Zenz T, Marioni JC, Buettner F, Huber W, Stegle O. Multi-Omics Factor Analysis-a framework for unsupervised integration of multi-omics data sets. *Mol Syst Biol* 2018; **14**: e8124 [PMID: 29925568 DOI: 10.15252/msb.20178124]

71 **Cai J**, Sun L, Gonzalez FJ. Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis. *Cell Host Microbe* 2022; **30**: 289-300 [PMID: 35271802 DOI: 10.1016/j.chom.2022.02.004]

72 **Pratt M**, Forbes JD, Knox NC, Bernstein CN, Van Domselaar G. Microbiome-Mediated Immune Signaling in Inflammatory Bowel Disease and Colorectal Cancer: Support From Meta-omics Data. *Front Cell Dev Biol* 2021; **9**: 716604 [PMID: 34869308 DOI: 10.3389/fcell.2021.716604]

73 **Zhuang X**, Tian Z, Li N, Mao R, Li X, Zhao M, Xiong S, Zeng Z, Feng R, Chen M. Gut Microbiota Profiles and Microbial-Based Therapies in Post-operative Crohn's Disease: A Systematic Review. *Front Med (Lausanne)* 2020; **7**: 615858 [PMID: 33585513 DOI: 10.3389/fmed.2020.615858]

74 **Lee JWJ**, Plichta D, Hogstrom L, Borren NZ, Lau H, Gregory SM, Tan W, Khalili H, Clish C, Vlamakis H, Xavier RJ, Ananthakrishnan AN. Multi-omics reveal microbial determinants impacting responses to biologic therapies in inflammatory bowel disease. *Cell Host Microbe* 2021; **29**: 1294-1304.e4 [PMID: 34297922 DOI: 10.1016/j.chom.2021.06.019]

75 **Lloyd-Price J**, Arze C, Ananthakrishnan AN, Schirmer M, Avila-Pacheco J, Poon TW, Andrews E, Ajami NJ, Bonham KS, Brislawn CJ, Casero D, Courtney H, Gonzalez A, Graeber TG, Hall AB, Lake K, Landers CJ, Mallick H, Plichta DR, Prasad M, Rahnavard G, Sauk J, Shungin D, Vázquez-Baeza Y, White RA 3rd; IBDMDB Investigators, Braun J, Denson LA, Jansson JK, Knight R, Kugathasan S, McGovern DPB, Petrosino JF, Stappenbeck TS, Winter HS, Clish CB, Franzosa EA, Vlamakis H, Xavier RJ, Huttenhower C. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* 2019; **569**: 655-662 [PMID: 31142855 DOI: 10.1038/s41586-019-1237-9]

76 **Imhann F**, Van der Velde KJ, Barbieri R, Alberts R, Voskuil MD, Vich Vila A, Collij V, Spekhorst LM, Van der Sloot KWJ, Peters V, Van Dullemen HM, Visschedijk MC, Festen EAM, Swertz MA, Dijkstra G, Weersma RK. The 1000IBD project: multi-omics data of 1000 inflammatory bowel disease patients; data release 1. *BMC Gastroenterol* 2019; **19**: 5 [PMID: 30621600 DOI: 10.1186/s12876-018-0917-5]

77 **Ludvigsson JF**, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; **11**: 450 [PMID: 21658213 DOI: 10.1186/1471-2458-11-450]

78 **Norris RP**, Dew R, Sharp L, Greystoke A, Rice S, Johnell K, Todd A. Are there socio-economic inequalities in utilization of predictive biomarker tests and biological and precision therapies for cancer? A systematic review and meta-analysis. *BMC Med* 2020; **18**: 282 [PMID: 33092592 DOI: 10.1186/s12916-020-01753-0]

79 **Spratt DE**, Chan T, Waldron L, Speers C, Feng FY, Ogunwobi OO, Osborne JR. Racial/Ethnic Disparities in Genomic Sequencing. *JAMA Oncol* 2016; **2**: 1070-1074 [PMID: 27366979 DOI: 10.1001/jamaoncol.2016.1854]

80 **Martin AR**, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet* 2019; **51**: 584-591 [PMID: 30926966 DOI: 10.1038/s41588-019-0379-x]

81 **Yeh VM**, Bergner EM, Bruce MA, Kripalani S, Mitrani VB, Ogunsola TA, Wilkins CH, Griffith DM. Can Precision Medicine Actually Help People Like Me? African American and Hispanic Perspectives on the Benefits and Barriers of Precision Medicine. *Ethn Dis* 2020; **30**: 149-158 [PMID: 32269456 DOI: 10.18865/ed.30.S1.149]

82 **Lynch JA**, Berse B, Rabb M, Mosquin P, Chew R, West SL, Coomer N, Becker D, Kautter J. Underutilization and disparities in access to EGFR testing among Medicare patients with lung cancer from 2010 - 2013. *BMC Cancer* 2018; **18**: 306 [PMID: 29554880 DOI: 10.1186/s12885-018-4190-3]

83 **Mills RH**, Dulai PS, Vázquez-Baeza Y, Sauceda C, Daniel N, Gerner RR, Batachari LE, Malfavon M, Zhu Q, Weldon K, Humphrey G, Carrillo-Terrazas M, Goldasich LD, Bryant M, Raffatellu M, Quinn RA, Gewirtz AT, Chassaing B, Chu H, Sandborn WJ, Dorrestein PC, Knight R, Gonzalez DJ. Multi-omics analyses of the ulcerative colitis gut microbiome link Bacteroides vulgatus proteases with disease severity. *Nat Microbiol* 2022; **7**: 262-276 [PMID: 35087228 DOI: 10.1038/s41564-021-01050-3]

84 **Zhang X**, Deeke SA, Ning Z, Starr AE, Butcher J, Li J, Mayne J, Cheng K, Liao B, Li L, Singleton R, Mack D, Stintzi A, Figeys D. Metaproteomics reveals associations between microbiome and intestinal extracellular vesicle proteins in pediatric inflammatory bowel disease. *Nat Commun* 2018; **9**: 2873 [PMID: 30030445 DOI: 10.1038/s41467-018-05357-4]

85 **Dai Y**, Pei G, Zhao Z, Jia P. A Convergent Study of Genetic Variants Associated With Crohn's Disease: Evidence From GWAS, Gene Expression, Methylation, eQTL and TWAS. *Front Genet* 2019; **10**: 318 [PMID: 31024628 DOI: 10.3389/fgene.2019.00318]

86 **Suskind DL**, Lee D, Kim YM, Wahbeh G, Singh N, Braly K, Nuding M, Nicora CD, Purvine SO, Lipton MS, Jansson JK, Nelson WC. The Specific Carbohydrate Diet and Diet Modification as Induction Therapy for Pediatric Crohn's Disease: A Randomized Diet Controlled Trial. *Nutrients* 2020; **12** [PMID: 33291229 DOI: 10.3390/nu12123749]

87 **Borren NZ**, Plichta D, Joshi AD, Bonilla G, Sadreyev R, Vlamakis H, Xavier RJ, Ananthakrishnan AN. Multi-"-Omics" Profiling in Patients With Quiescent Inflammatory Bowel Disease Identifies Biomarkers Predicting Relapse. *Inflamm Bowel Dis* 2020; **26**: 1524-1532 [PMID: 32766830 DOI: 10.1093/ibd/izaa183]

88 **Liu J**, Fang H, Hong N, Lv C, Zhu Q, Feng Y, Wang B, Tian J, Yu Y. Gut Microbiome and Metabonomic Profile Predict Early Remission to Anti-Integrin Therapy in Patients with Moderate to Severe Ulcerative Colitis. *Microbiol Spectr* 2023; **11**: e0145723 [PMID: 37199618 DOI: 10.1128/spectrum.01457-23]

89 **Huang Q**, Zhang X, Hu Z. Application of Artificial Intelligence Modeling Technology Based on Multi-Omics in Noninvasive Diagnosis of Inflammatory Bowel Disease. *J Inflamm Res* 2021; **14**: 1933-1943 [PMID: 34017190 DOI: 10.2147/JIR.S306816]

90 **Gonzalez CG**, Mills RH, Zhu Q, Sauceda C, Knight R, Dulai PS, Gonzalez DJ. Location-specific signatures of Crohn's disease at a multi-omics scale. *Microbiome* 2022; **10**: 133 [PMID: 35999575 DOI: 10.1186/s40168-022-01331-x]

91 **Xu S**, Li X, Zhang S, Qi C, Zhang Z, Ma R, Xiang L, Chen L, Zhu Y, Tang C, Bourgonje AR, Li M, He Y, Zeng Z, Hu S, Feng R, Chen M. Oxidative stress gene expression, DNA methylation, and gut microbiota interaction trigger Crohn's disease: a multi-omics Mendelian randomization study. *BMC Med* 2023; **21**: 179 [PMID: 37170220 DOI: 10.1186/s12916-023-02878-8]

92 **Gao X**, Sun R, Jiao N, Liang X, Li G, Gao H, Wu X, Yang M, Chen C, Sun X, Chen L, Wu W, Cong Y, Zhu R, Guo T, Liu Z. Integrative multi-omics deciphers the spatial characteristics of host-gut microbiota interactions in Crohn's disease. *Cell Rep Med* 2023; **4**: 101050 [PMID: 37172588 DOI: 10.1016/j.xcrm.2023.101050]

93 **Baran NM,** Aden K, Tran F, Ira Blasé J, Conrad3 C, Nikolaus S, Schreiber S, Rosenstiel P. Early Molecular Signatures of Therapeutic Response To Vedolizumab Therapy In Inflammatory Bowel Disease Patients Identified Using A Longitudinal Multi-Omics Approach. *United European Gastroenterol J* 2022; **10** [DOI: 10.1016/s0016-5085(22)61889-4]

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**Figure Legends**



**Figure 1 The interplay of various omics in inflammatory bowel disease.**



**Figure 2 Simplified pathway to precision medicine in inflammatory bowel disease.** IBD: Inflammatory bowel disease. Parts of Figure 2 were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/Licenses/by/3.0/).

**Table 1 Studies utilizing multiomics in inflammatory bowel disease**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **No.** | **Ref.** | **Type of study** | **Number of participants** | **Type of omics utilized** | **Results** |
| 1 | Lloyd-Price *et al*[75] | Cohort study | 132 IBD | Microbiome; genome; metagenome; meta; transcriptome; metabolome profiles; proteome | Found functional dysbiosis in the gut microbiome, changes in metabolite pools, and increased levels of antibodies in serum during periods of inflammatory bowel disease activity |
| 2 | Mills *et al*[83] | Cohort study | -40 UC, -validation cohort: 73 UC, 117 CD, 20 controls | Proteome; metaproteome; metabolome; metagenome; meta peptidome | UC patients with active disease had increased protease activity that originated from the bacterium *Bacteroides vulgatus* |
| 3 | Zhang *et al*[84] | Cohort study | 25 CD, 22 UC, 24 controls | Metaproteome; microbiome | Identified functional alterations of microbiome and associated microbial proteins in the intestinal mucosa in new-onset pediatric IBD patients which contributed to abnormal host-microbiota interactions |
| 4 | Lee *et al*[74] | Prospective study | 108 CD, 77 UC | Metabolome; microbiome; metagenome; proteome | Microbial, metagenomic diversity and metabolomics (serum secondary bile acid concentrations) predicted response in moderate-to-severe Crohn’s disease or ulcerative colitis patients initiating anti-cytokine therapy (anti-TNF or -IL12/23) or anti-integrin therapy |
| 5 | Dai *et al*[85] | Prospective study | 5956 CD, 21770 controls | Genome; epigenome; transcriptome | Identified strongly associated CD genes involved in immune response, MHC class II receptor activity, and immunological disorders. Involvement of constitutive photomorphogenesis 9 signalosome in CD pathogenesis. Interactions among CD genes with CD drug target genes |
| 6 | Suskind *et al*[86] | Randomized controlled trial | 10 CD | Microbiome; metagenome; metaproteome; metabolome | Diet had a positive effect on CD patient symptoms and inflammation; Specific exclusionary diets were associated with a better resolution of inflammation |
| 7 | Borren *et al*[87] | Cohort study | 108 CD, 56 UC | Proteome; metabolome; microbiome | Identified proteomic, metabolomic, and microbiome biomarkers that characterized a proinflammatory state in quiescent IBD patients and predicted clinical relapse |
| 8 | Liu *et al*[88] | Prospective study | 42 UC, 11 controls | Metabonome; microbiome | Identified that the combination of Verrucomicrobiota, butyric acid, and isobutyric acid improved the prediction of early remission to anti-integrin therapy |
| 9 | Huang *et al*[89] | Cohort study | 140 CD, 73 UC, 86 controls | Metagenome; meta transcriptome; proteome; metabolome; virome; microbiome | Established artificial intelligence models that can subtype IBD with high accuracy using simple noninvasive fecal biomarkers and avoiding invasive procedures |
| 10 | Mishra *et al*[60] | Cohort study | 37 IBD | Genome; epigenome | Identified biomarkers of early shifts in gene expression and DNA methylation for early prediction of anti-TNF treatment success |
| 11 | Gonzalez *et al*[90] | Cohort study | 200 IBD | Microbiome; metabolome; metaproteome; metagenome | Identified colonic- and ileal-isolated CD subtypes had different pathologies. Colonic CD was similar to ulcerative colitis with neutrophil and Bacteroides vulgatus involvement while Ileal-isolated CD had a bile acid-driven profile |
| 12 | Xu *et al*[91] | Cohort study | Discovery: 6 datasets, Validation: 46 CD, 44 controls | Genome; transcriptome; Epigenome; microbiome | Identified that CD onset results from a number of oxidative stress genes through DNA methylation, gene expression, and host-microbiota interactions |
| 13 | Gao *et al*[92] | Cohort study | 30 CD, 5 controls | Proteome; microbiome; metagenome | Identified alterations in proteins, microbiome, and metabolic processes across multi-tissues in CD patients that are imprinted in serum and fecal samples as potential diagnostic biomarkers, allowing a non-invasive precision diagnosis |
| 14 | Baran *et al*[93] | Cohort study | 18 IBD | Epigenome; transcriptome; genome | Therapeutic response causes transcriptional changes in the mucosa and early changes in gene expression in peripheral blood that are regulated epigenetically |

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn’s Disease; IL: Interleukin; TNF: Tumor necrosis factor.