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Integration and implementation of precision medicine in the multifaceted Inflammatory bowel disease

IBD & 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 conduction, data collection, data utilization, interpretation, and analysis. This review aims to describe the current literature on precision medicine, its multi-omics approach, and future directions for its application in IBD.

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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 multi-omics 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. 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* 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 and Chron's disease is increasingly evolving, mainly focusing on its genome, exposome, microbiome, immunome, and many other 'omics' approaches. Thomas *et al* 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 multi-omics 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. 3. Enhancing existing and creating novel molecular technologies to facilitate precision medicine.

We can achieve this through advances in multi-omics 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.

Methods and materials

We conducted a review of existing literature in PubMed and Google Scholar to find relevant studies with information on multi-omics 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, inflammatory bowel disease, 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 (GWAS) 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 inflammatory bowel disease (IBD) encompass various pathways, including microbial sensing (NOD2, CARD9, RIPK2), maintenance of intestinal barrier function (C1orf106, HNF4A), signaling within the innate and adaptive immune systems (NLRP7, IL18RAP, CD28, IFNG, PTPN22, STAT4, IL6ST, IL23R, RORC, IL17RA), fibrosis development (OSMR, SMAD3), and cellular homeostasis (ATG16L1, RNF186, ERGIC1). [7] Despite the advances in genetic pathways, very 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 GWAS studies of 29,838 patients by Cleynen *et al*, 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. ▪

Genome-wide association studies (GWAS) 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 fibro stenosis 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]. The IL3R has become a therapeutic agent for CD. [12] Studies have utilized genome basis to identify patients that benefit from hematopoietic stem cell transplantation and mesenchymal stem cell transplantation (HSCT) in patients with very early onset IBD and those with inborn errors of immunity.[13][14][15][16] Patients with genetic deficiencies such as IL-10, IL-10 receptor, and XIAP deficiencies benefitted from HSCT.[17][18][13][17] It also identifies mutations such as STXBP2, TTC7A, and EPCAM genes that will not benefit from particular therapies.[19][20][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 exposures influence 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* 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* 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 *et al* published data using the information of IBD patients from a UK 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* found that inflamed and non-inflamed colonic mucosa in inflammatory bowel disease 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

It is defined as all encountered exposures in the lifetime of an individual beginning from conception. There are endogenous exposomes 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 inflammatory bowel disease [4]. According to Lamb *et al*, it is the environmental factors that influence IBD pathogenesis. "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, veggies, 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 Crohn's disease (CD). As per the findings of Svolos *et al*, 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* 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* 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][38][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. Massodi *et al* described altered Poly unsaturated 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* 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 in IBD.[46] Titz *et al* 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 Crohn's disease (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* 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 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 multi-omics. 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 multi-omics 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 this 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 multi-omics in inflammatory bowel disease 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.[51][3]

Cleynen *et al* conducted a large genotype association study in patients with IBD using genotype-phenotype associations from 156-154 gene variants. They found ileal Crohn's disease, colonic Crohn's disease, 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* 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 (TDM), 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 diseases 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 genome-wide association studies. 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 inflammatory bowel disease, emphasizing the importance of employing methodologies 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 (MDPs) 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.[51][3][56].

The primary obstacle in the development and validation of precision medicine interventions for inflammatory bowel disease lies in the extensive variability observed in the disease's 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 (PROs) and non-invasive 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 Fecal calprotectin (FC) levels predicted disease relapse within the next 2 to 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 Inflammatory Bowel Disease. 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 inflammatory bowel disease. [50] The first study investigated the role of NOD2 variants in the pathogenesis of Crohn's disease 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 glycoprotein 130 (gp130)-STAT3 axis, which may contribute to the pathogenesis of Crohn's disease. 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 anti-cytokine 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 (EMRs), 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 in integrating it into patient profiles. Planned investigations with multi-country 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. ■ According to Valles Colomer et al, the use of microbiology (Meta-omics) has allowed the analysis of certain Bacteria present in people with IBD. In normal flora, the use of 16 S 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*, the use of machine learning approaches by using Artificial Intelligence and algorithms creates patterns not seen before in the management of Inflammatory bowel disease.[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-TNF Therapy in Crohn's Disease (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 non-response 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 non-remission 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 ulcerative colitis (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 (C-reactive protein) were identified as the sole additional independent predictor in this context. [59]Single-cell gene expression technologies have been employed 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*, 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 adenosine triphosphate (eATP), 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 eATP 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]

Multi-omics 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 multi-omics 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 vs. non-responders to anti-TNF induction using single transcripts such as the OSM, OSMR, or TREM1[61]. A study also differentiated responders vs. non-responders 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 employed 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][64][65].

Waljee *et al* 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* 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 genome-wide association studies based on patient phenotypes, response to treatment, and prognosis.[67]

Finally, treatment with biologics can alter the transcriptome profiles of Crohn's patients distinguishing naive 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, sub-

categorization, treatment during the changing disease course, prognostication, and follow-up.

Multi-omics

In recent decades, advances in technology have enabled the comprehensive profiling of the human gut microbiome through meta-omics methodologies. The power of functional meta-omics lies in its potential to identify molecular biomarkers that can assist with non-invasive screening and diagnosis, and treatment response. Data integration is the process of combining multi-omics data.[69][70] Table 1 describes studies consulting using multiple layers of multi-omics 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 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 meta-omics has revealed similar metabolic dysregulation in

both IBD and colorectal cancer (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 anti-cytokine 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 anti-cytokine 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 (IBDMDB) study, part of the Human Microbiome Project Phase 2 (HMP2), investigated the gut microbiome of inflammatory bowel disease (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 naive 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. (Zhao *et al*) The IBD prognosis study, 1000IBD project, Swedish IBD quality register, and the Dutch IBD biobank are similar multi-omics integration studies and datasets for IBD.[76][52][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 pre-diagnostic stages, have been established. Ongoing multi-omics 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*, those with low socio-economic status were 17% less likely to be treated with novel precision medicine therapies for cancer.[78] Spratt *et al* describes in his study of 5729 genomic sequencing samples that only 12 % were African American population and 3% were Hispanic and 3% were Asian. This overrepresents the white population and underrepresents 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* 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* 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 multi omics 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 socio-economic 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 socio-economic status is essential to help in the recruitment of underrepresented samples and ensure results are generalizable.

Precision medicine is very 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 size 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 misuse of data.

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 GWAS 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 UK 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 tumor necrosis factor-like ligand 1A, 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 muti-omics to further IBD management and deliver precision medicine with next-level care in IBD patients for the current and future should be targeted.

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