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Clinical value of multi-omics-based biomarker signatures in inflammatory bowel diseases: challenges and opportunities

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Abstract

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are complex and heterogeneous diseases characterized by a multifactorial etiology,

therefore demanding a multimodal approach to disentangle the main pathophysiological components driving disease onset and progression. Adoption of a *systems biology* approach is increasingly advocated with the advent of multi-omics profiling technologies, aiming to improve disease classification, to identify disease biomarkers and to accelerate drug discovery for patients with IBD. However, clinical translation of multi-omics-derived biomarker signatures is lagging behind, since there are several obstacles that need to be addressed in order to realize clinically useful signatures. Multi-omics integration and IBD-specific identification of molecular networks, standardization and clearly defined outcomes, strategies to tackle cohort heterogeneity, and external validation of multi-omics-based signatures are critical aspects. While striving for *personalized medicine* in IBD, careful consideration of these aspects is however needed to adequately match biomarker targets (e.g. the gut microbiome, immunity or oxidative stress) with their corresponding utilities (e.g. early disease detection, endoscopic and clinical outcome). Theory-driven disease classifications and predictions are still governing clinical practice, while this could be improved by adopting an unbiased, data-driven approach relying on molecular data structures integrated with patient and disease characteristics. In the foreseeable future, the main challenge will lie in the complexity and impracticality of implementing multi-omics-based signatures into clinical practice. Still, this could be achieved by developing easy-to-use, robust and cost-effective tools incorporating omics-derived predictive signatures and through the design and execution of prospective, longitudinal, biomarker-stratified clinical trials.

Keywords: inflammatory bowel diseases; multi-omics; biomarkers; systems biology; personalized medicine; validation.

Abbreviations

AUC	area under the curve
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRP	C-reactive protein
GIEQ	Groningen IBD Environmental Questionnaire
GINQ	Groningen IBD Nutritional Questionnaire
HBI	Harvey-Bradshaw Index
HMP	Human Microbiome Project
IBD	Inflammatory Bowel Disease
PROBAST	Prediction model Risk Of Bias ASsessment Tool
SCCAI	Simple Clinical Colitis Activity Index
SPIRIT	Selecting End PoInts foR Disease-ModIfication Trials
STRIDE	Selecting Therapeutic Targets in Inflammatory Bowel Disease
TDM	therapeutic drug monitoring
TNFα	tumor necrosis factor alpha
UC	Ulcerative colitis

Introduction

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic immune-mediated diseases of the gastrointestinal (GI) tract, characterized by a broad clinical heterogeneity and a high degree of pathophysiological complexity [1]. CD is characterized by transmural ulcerative inflammation that can occur in any part of the GI tract, whereas UC is marked by rather superficial inflammation that is limited to the colon. Although the exact etiology of IBD remains elusive, an interplay between genetic background, gut microbiota, immunity and environmental factors (e.g. lifestyle, diet) is considered to underlie its pathogenesis [2,3]. The peak age of onset lies within the second to fourth decade of life, and the disease course typically alternates between episodes of quiescent and active disease, which are difficult to predict and to adequately treat. The complex, unpredictable and heterogeneous nature of IBD complicates early detection of the diagnosis, monitoring of disease activity and -complications, and prediction of disease course and treatment response. This highlights the urgent need for *biomarkers*: objectively measured indicators of (ab)normal biological processes or -systems or pharmacologic responses to therapeutic interventions [4,5].

In the context of IBD, biomarkers are already used for a variety of clinical purposes, and can be derived from several determinants of IBD susceptibility, e.g. the host genome, transcriptome, proteome, immune system, or gut microbiome, or from pathogenic mechanisms such as inflammation, oxidative stress and fibrosis [6]. Given the complex pathobiology of IBD, insights from multiple layers of biological data, referred to as a *systems biology* approach, are required to unravel disease pathogenesis [7,8]. In addition, the therapeutic armamentarium of IBD covers drugs targeting many different molecular pathways, whereas we lack the knowledge to make educated decisions about which drug is best for each individual patient. Systems biology

consists of holistic and mathematical modeling of complex biological systems [9,10]. Recent technological (e.g. next-generation sequencing, high-density protein arrays) and computational (e.g. machine learning, artificial intelligence) advances have facilitated the integration of 'big data', enabling the establishment of molecular constructs that are specific to IBD [11,12]. However, the investigation of such big complex molecular data entities should be accompanied by careful integration of patient phenotypes, clearly defined outcomes, and independent validation in order to achieve clinically translatable, omics-based biomarker signatures.

In this review, we highlight the potential of multi-omics profiling for biomarker discovery in IBD, followed by an outline of key challenges and unmet needs warranting attention in this context. Finally, we outline some key examples of recent developments in clinical implementation of multi-omics-based biomarker signatures in IBD. These opportunities to improve disease prediction using multi-omics data may eventually translate into improved outcomes for patients with IBD.

The promise of multi-omics-based biomarker signatures in IBD

The complex, heterogeneous and multifactorial nature of IBD rationalizes a systems biology approach for its management. The advent of multi-omics profiling technologies such as genomics (whole-genome genotyping [WGS] using ImmunoChip or Global Screening Array sequencing e.g. whole-exome sequencing [WES]), transcriptomics (e.g. bulk RNA-sequencing), proteomics (e.g. proximity extension assay [PEA] technology, modified-aptamer binding technology or mass-spectrometry-based techniques) or metagenomics (metagenomic shotgun sequencing [MGS], among others, allows for a better understanding of IBD pathophysiology. An

increasing number of multi-omics studies revealed signatures predictive of disease phenotypes, disease course, therapeutic success, and prognosis in patients with IBD [11,13-22]. Despite the experimental and computational advances made in this field, the exact clinical utility of multi-omics-derived signatures, however, remains poorly characterized, mainly due to a lack of their integration, sparsity, and international synchronization. Leveraging machine learning-based methods and bioinformatic tools, multi-omics profiles carry potential to improve disease classification and prediction by interrogating the enormous pile of biological data arising from them. Unlike traditionally-used theory- or symptom-based approaches for disease classification (e.g. the Montreal classification, Rutgeerts score), molecular data-driven biomarker discovery may reveal the key pathophysiological components of IBD, using molecular data structures while relying on detailed phenotypes (**Figure 1**).

An unbiased generation of composite biomarker signatures may confer predictive accuracy in relation to disease activity, complications or therapeutic response, enabling delivery of the most effective treatment to every patient with IBD [23]. In addition, multi-omics characterization could inspire functional studies to acquire mechanistic insight into the biological relevance of the identified signatures and thereby increase their potential utility [8]. Clinical translation of multi-omics-derived signatures could guide physicians in making treatment decisions for their patients, based on estimated individual therapeutic efficacy, following the concept of *personalized medicine*. Yet, this approach has not translated into robust clinical implementations, since there are several unresolved issues impeding clinical integration. A key issue pertains to interindividual patient variation that keeps explaining the majority of data variation in multi-omics studies, risking that potentially important observations are masked within subject-to-subject differences [12]. Many variables may affect the dynamics of multi-

omics configurations, requiring prospective longitudinal studies and accurate recordkeeping during the disease course of patients to comprehensively model interactions between biological features, host characteristics and clinical outcomes. Furthermore, stratification for specific clinical parameters alongside validation of identified signatures in independent cohorts is eventually needed to pinpoint to functionally relevant markers of IBD.

Challenges and pitfalls complicating clinical translation of multi-omics-based biomarker signatures

Despite the advances made in multi-omics-driven biomarker discovery for IBD, there are several obstacles that need to be addressed in order to realize clinical translation of multi-omics-based signatures. Key aspects in this context include the need for multi-omics data integration and network analysis, phenotypic patient stratification, standards and definitions for relevant disease modification outcomes, and external validation of predictive signatures.

Integrative multi-omics and molecular networks specific to IBD

Single-omics characterization of IBD is well-established, and this has provided insights into the functional dysregulation and distinct alterations in the genome, gut microbiome, transcriptome, proteome, metabolome, among others, in patients compared to non-IBD controls. Although valuable knowledge has been gained in these studies, integration of multi-omics layers would give more comprehensive insight into the complexity and key nodes of interactions. However,

there are only few studies available that integrated at least two different omics datasets of patients with IBD, as was recently reviewed elsewhere [7]. A key example includes the HMP2/iHMP project, in which 132 patients were followed for over a year and longitudinally sampled for metagenomics, metatranscriptomics, metaproteomics and metabolomics profiling [11]. Its unique study design allowed to identify the dynamic changes in these complementary molecular profiles, which proved to be of much greater magnitude than were cross-sectional differences among the studied phenotypes. Although many distinct features were identified, and some demonstrated temporal stability, independent validation was lacking. Another aspect relevant to integration of multi-omics data includes the establishment of IBD-specific molecular network information. Although many types of interactions (e.g. microbe-metabolite, gene-protein, microRNA-mRNA) would provide pathophysiological insights, they are often not context-specific, but rather generic, usually as a result of experimental conditions. Therefore, more targeted approaches are required to profile IBD-specific interactions leveraging appropriate bioinformatic tools [7].

Bioinformatic challenges associated with integrative multi-omics

One of the key challenges associated with performing integrative multi-omics studies pertains to the identification of tailored bioinformatics approaches to tackle complex data structures such as multi-omics datasets. One of the key challenges in this regard is the aforementioned interpatient variation that keeps to explain to majority of multi-omics data variation, which reflect the problem that a wide variety of variables affect the dynamics of multi-omics data configurations [12]. On the other hand, missing data and the requirement for bioinformatic data imputation decrease the accuracy of the acquired data, and thereby may introduce bias [10]. There are also

more statistical obstacles such as insufficient power, class imbalances, or data sparsity, that may complicate or exclude the use of certain bioinformatic approaches and/or affect interpretation of integrative analyses. In addition, there may be a lack of biological granularity in that bulk sequencing of DNA and RNA extracted from biopsies or blood is performed in many studies, whereas cell type-specificity driving the pathophysiology of IBD becomes increasingly apparent. Importantly, there are also more practical bioinformatic challenges such as the availability and practicality of data storage and data analysis workflows alongside the growing need for more volume and computational power, respectively. In this respect, the implementation of more user-friendly software platforms e.g. to facilitate clinical IBD researchers in handling complex multi-omics datasets would be important to better translate these efforts into clinical practice. Finally, there is a lack of consensus regarding which computational methodologies are preferred over others in dealing with specific high-throughput multi-omics datasets. Closer collaboration between experienced bioinformaticians and clinical IBD researchers is crucial to facilitate performance of multi-omics integration studies and establish consensus-based recommendations or even guidelines for multi-omics data-analysis.

Phenotypic patient stratification to account for key clinical confounders

An important challenge pertaining to integrative omics analyses constitutes interpatient variation that contributes to the majority of data variation, which may jeopardize observations of potentially important pathophysiological features that may otherwise remain unidentified. Although the list of potential clinical confounding variables is long, and many remain context-dependent, some key factors deserve mentioning in the context of clinical multi-omics integration in IBD (**Figure 2**).

First, an important but often overlooked aspect is the use of concomitant medication. A striking example includes corticosteroids, which may confound biomarker discovery mainly because of their inherently strong anti-inflammatory effects, which may affect disease activity and therapeutic response [26]. Although it remains difficult to pinpoint the exact effects on certain molecules, medication usage may result in inaccurate biomarker evaluation. Similarly, other elements of clinical history may be critical, for example disease duration which is generally inversely associated with therapeutic success rates [27]. Moreover, medication history impacts the plausibility of responding to novel treatments, i.e. previous use of certain medications such as TNF-α-antagonists decreases the chance of responding to a subsequent therapy [28]. This phenomenon is illustrated by studies that investigated the molecular changes upon vedolizumab and ustekinumab treatments, which generally exert higher anti-inflammatory effects, i.e. showing better results, in patients who are naive to TNF-α-antagonists [29,30]. As such, not only concomitant medication usage but also previous drug exposure and disease history are important factors to account for in biomarker studies. Third, the degree of intestinal inflammation, which relentlessly fluctuates in patients, impacts physiological processes such as gene expression, protein production, and paracrine communication, and triggers structural (tissue) changes. As a consequence, querying multi-omics data for biomarkers may become problematic, since the biological constituents under investigation (i.e. gene expressions, proteins or metabolites) may change upon inflammation and conceal the true objectivity of a particular signature (i.e. being related to the pathophysiology of the disease or to a pharmacological mechanism). Considering this, any particular multi-omics signature should ideally outperform classical parameters of inflammation such as C-reactive protein (CRP) or fecal calprotectin, which have repeatedly been associated with relevant outcomes such as therapeutic response [31,32]. This emphasizes the

need for investigating multi-omics signatures in both inflamed and non-inflamed situations to test this potential inflammatory dependency. Fourth, the environmental contingency of a study population should be carefully considered. Differences in habitual diet and environmental exposures may have profound effects on disease pathobiology, and may thus impact on a specific layer of biological data under evaluation [3]. Finally, drug exposure is important since insufficient exposure could lead to falsified conclusions about the performance of multi-omics-derived predictive signatures. For instance, in studies searching for biomarkers of therapeutic response, it would be important to confirm that patients achieve roughly equal levels of drug exposure since some might otherwise be regarded as non-responders due to pharmacodynamic failure. The implementation of therapeutic drug monitoring (TDM) is crucial to address this issue by excluding the possibility of insufficient drug exposure as reason for therapeutic failure.

Setting standards and definitions for clinical outcomes to enhance effectivity of multi-omics-based biomarker signatures

Various clinical outcomes have been used in multi-omics-driven biomarker evaluation, e.g. disease activity, therapeutic response or fibrotic disease complications [11,14,15,17]. These, in turn, result in a variety of study endpoints, e.g. the degree of endoscopic disease activity, the height of clinical scores defining response to therapy, or intestinal thickness as indicator of fibrosis. However, this heterogeneity in outcome assessments does not fully appreciate the pathophysiological complexity and clinical heterogeneity of IBD, nor facilitates the prevailing aim of modifying disease course and changing prognosis for patients with IBD [33].

At single-center level, there is often already a lack of synchronization of study outcome definitions in clinically-oriented multi-omics studies, which may have practical reasons. For example, standardized endoscopic evaluation of disease activity after induction therapy with biologics varies across hospitals: while in some this is never practiced, in others it is performed at pre-specified time intervals during therapy irrespective of the patient's clinical status. Moreover, disagreement may arise in scoring of clinical disease activity (e.g. using CDAI, HBI or SCCAI scores) or with regard to criteria that should be adopted for defining clinical response to therapy. Such scenarios may result in severe under- or overestimation of the real value of multi-omics-based biomarker signatures and subsequently complicate their validation.

At multi-center level, the heterogeneity in outcome definitions of multi-omics-driven biomarker studies further expands. In this respect, defining endoscopic disease activity is a striking example. While some centers employ pre-specified cut-offs of specific endoscopic scores to define endoscopic remission, others take the absence of any ulcerations (*mucosal healing*) as sole criterion [34]. Although mucosal healing is increasingly recognized as important therapeutic endpoint in clinical trials - since it strongly associates with sustained remission and resection-free survival [35-37] -, there is not yet full consensus on using it as definite endoscopic outcome, because the evidence for efficacious induction of mucosal healing varies by type of treatment while interpatient variation complicates efforts to achieve it [38]. To overcome this lack of uniformity, endoscopic assessments are increasingly subject to 'central reading', i.e. independent, off-site, blinded review of imaging endpoints in clinical trials [39].

From a statistical perspective, there is also much heterogeneity in relating clinically relevant outcomes to multi-omics-based signatures. For example, dichotomizing outcomes for statistical convenience may lead to a potential loss of information by removing fine-grained,

intra-category information that may more accurately represent true biological scales [40]. Machine learning-driven models often used in multi-omics studies may suffer from these efforts since it may result in underestimation of the true predictive value of certain signatures [41]. Studies are warranted to investigate the non-inferiority of using either continuous or categorical definitions for each unique outcome, including studies focusing on the minimal differences in outcome that would be considered as clinically (or biologically) relevant.

To achieve more international consensus on the definition of disease modification outcome measures, several collaborative efforts (e.g. the SPIRIT and STRIDE initiatives [33,42,43]) are aimed at establishing objective, holistic, multi-dimensional outcome assessment by following a patient-centered approach that would be more compatible with IBD.

External validation of multi-omics-based biomarker signatures

To date, few multi-omics data integration studies in IBD performed independent, external validation of their key findings (although there are exceptions [13]). Instead, cross-validation procedures (i.e. train- and test splits from the same cohort) are often performed when an independent replication cohort is lacking. However, before any multi-omics-based biomarker signature could be suitable for clinical implementation, it is important to validate its utility in diverse populations, e.g. ethnic and geographically distinct cohorts including patients with differing genetic background and environmental exposures. Since it is likely that such factors will at least partially determine the behavior of identified signatures (since they influence human biology), external validation is required to test their generalizability and reproducibility. Ideally, this should be performed in large, well-characterized cohorts of patients. Currently, there are

large ongoing efforts attempting to realize this multi-omics testing on a global level, e.g. the IBD Plexus® or the COLLIBRI and 3TR consortia. This may bridge the gap between the development of multi-omics-driven signatures and their clinical implementation, while also avoiding waste of extensive research efforts in finding potential biomarkers.

It is important to develop criteria for appropriate external validation studies (**Figure 3**). For example, the fraction of patients undergoing or achieving the "event" (e.g. response to treatment) and its proportionality to the discovery cohort should be carefully considered to avoid model overfitting and to allow the adjustment for confounding variables [44,45]. This is crucial as it may impact model performance, and the baseline risk of the event may differ across populations. In addition, profiling of multi-omics-based signatures should ideally be performed under similar conditions to avoid interference with predictive performances [46]. Furthermore, the assessment of baseline patient and disease characteristics between discovery and external validation cohorts is important to avoid large differences in "case mix", referring to the distribution of predictor values that may influence the predictive performance of the signature under investigation [47,48]. This bias could be addressed by comparing baseline characteristics between discovery and validation cohorts to determine the degree of cohort similarity and generalizability. In general, the more homogeneous and similar both cohorts are, the higher the likelihood of successful validation will become. Striving for this cohort homogeneity is especially important for validation of rather dynamic biomarkers (e.g. proteomic- or transcriptomic-based biomarkers) to reduce the risk of confounding. Statistical frameworks have been developed to allow comparisons of baseline characteristics for external validation studies by calculating (dis)similarity metrics between cohorts [49]. In addition, bias risk estimation tools have been

developed that may help to determine whether a particular prediction model is suitable for external validation (e.g. the Prediction model Risk Of Bias ASsessment Tool (PROBAST) [50]).

Towards clinical implementation of multi-omics-derived biomarker signatures

The main challenge associated with multi-omics-driven biomarker discovery lies in the complexity and impracticality of such data-driven approaches in clinical practice. Clinical integration of multi-omics profiles entails financial, legal, ethical, and other logistic constraints, without even considering potential strategies [51,52]. Thus, the development of easily applicable, robust and cost-effective clinical implementations incorporating multi-omics-derived biomarker signatures should be prioritized. Several examples exist that illustrate the potential of multi-omics data integration to improve disease classification, to predict disease prognosis and to individualize treatment. For example, a recent study established a pharmacogenetic passport integrating individual genetic variants to predict the risk of adverse drug responses such as thiopurine-induced myelosuppression, -pancreatitis and immunogenicity of TNF-α-antagonists [53]. Such pharmacogenetic tools may aid in providing personalized treatment recommendations by optimizing drug selection and minimizing drug toxicity, resulting in a potential reduction of therapeutic failure and costs. Another example constitutes the development of a "transcriptomics-based blood-derived 17-gene prognostic biomarker" that could predict prognosis in newly diagnosed patients with IBD [54]. This $CD8^+$ T-cell gene expression signature accurately identified patients who experienced an aggressive disease course characterized by earlier disease recurrence and a higher frequency of disease flares [55]. Importantly, this signature was subsequently replicated in multiple prospective, independent

replication cohorts from the UK, and this has culminated into the initiation of the first-ever biomarker-stratified clinical trial in IBD [56]. This trial will evaluate whether this transcriptional signature is indeed capable of improving clinical outcomes by facilitating personalized medicine for patients with CD. Insofar, most of the currently available -omics studies are single-omics studies, while multi-omics integration studies hold promise to find more accurate biomarkers. The potential value of clinical multi-omics integration became particularly evident from a recent study integrating serum metabolomics, proteomics and fecal metagenomics data of patients with IBD [57]. Two distinct microbial signatures were identified that were able to characterize a subset of patients who would benefit more from anti-cytokine therapy compared to anti-integrin therapy. The addition of multi-omics information to their prediction models resulted in an astonishing increase in predictive accuracy: while a baseline model solely containing clinical information and serum inflammatory markers reached an area under the curve (AUC) of 0.62, the inclusion of multi-omics profiles dramatically increased this to 0.96 for predicting therapeutic response. Although external validation is required before application in clinical practice could ensue, these examples illustrate that the field of multi-omics-driven biomarker discovery is rapidly advancing and may particularly improve responses to inflammation-targeted therapies in IBD [58]. The promise of multi-omics integration and validation is supported by successful efforts like those reported in the field of oncology. For instance, an integrated microRNA-mRNA global profiling approach has previously been leveraged to identify microRNAs that were independently associated with prognosis in patients with breast cancer [59]. Other examples include the WINTHER and SPRING trials that tested the use of integrative multi-omics-based biomarker signatures to improve treatment strategies for patients with (non-small cell lung) cancer [60,61]. Therefore, also in the IBD field, it is important to continue

searching for biomarkers since this will help healthcare providers to make accurate therapeutic decisions already at first disease presentation (e.g. deciding on type of biological therapy), further decreasing the rates of therapeutic non-response.

Concluding remarks

Unraveling the pathophysiological complexity of a heterogeneous disease like IBD necessitates a systems biology approach which could be implemented using extensive and integrative multi-omics characterization at different levels of biological organization. Multi-omics-based biomarker signatures not only carry potential to advance our understanding of disease pathophysiology and accelerate drug discovery, shifting our focus to clinical integration of these signatures by developing clinical implementations could eventually improve disease outcomes for patients with IBD. Characteristics of multi-omics signatures may also inspire the scientific community to develop new theories about the pathways associated with disease activity, therapeutic response, or any other clinical utility. A subsequent translation of these conceptualizing efforts may promote the design of functional studies that could help to gain mechanistic insight into the biological relevance of each signature and fuel its evidence-based grounds. For example, organoids or advanced gut-on-a-chip models could be used to validate transcriptional signatures, and gnotobiotic mice could be used to validate functional effects of gut microbial signatures. Identification of the causal mechanisms behind multi-omics-derived signatures is important, since experimental validation is usually lacking from initial discovery studies. Similarly, future studies are needed to understand the long-term durability of multi-omics signatures, i.e. the extent to which those signatures maintain their predictive value over time. Here we attempted to provide a concise report of the challenges and opportunities

originating from the application of multi-omics profiling technologies in IBD, with special emphasis on the need for integration and network analysis, consideration of key clinical confounders, setting standards and definitions of clinically relevant outcomes, and the need for external validation of multi-omics signatures. Molecular data-driven clinical implementations or 'clinical omics integration' hold great potential by unraveling IBD pathobiology and addressing unmet clinical needs. Securing appropriate study designs, the distance between the clinic and laboratory (e.g. efficient transport of biomaterials to the site of analysis), data and the underlying infrastructure, financial and bioinformatic resources, and while employing standardized outcomes, methodologies and technologies, this strategy could become reality and anchored in IBD care.

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