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Results of the Seventh Scientific Workshop of ECCO: Precision Medicine in IBD—What, Why, and How

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Abstract

Many diseases that affect modern humans fall in the category of complex diseases, thus called because they result from a combination of multiple aetiological and pathogenic factors. Regardless of the organ or system affected, complex diseases present major challenges in diagnosis, classification, and management. Current forms of therapy are usually applied in an indiscriminate fashion based on clinical information, but even the most advanced drugs only benefit a limited number of patients and to a variable and unpredictable degree. This 'one measure does not fit all' situation has spurred the notion that therapy for complex disease should be tailored to individual patients or groups of patients, giving rise to the notion of 'precision medicine' [PM].

Inflammatory bowel disease [IBD] is a prototypical complex disease where the need for PM has become increasingly clear. This prompted the European Crohn's and Colitis Organisation to focus the Seventh Scientific Workshop on this emerging theme. The articles in this special issue of the *Journal* address the various complementary aspects of PM in IBD, including what PM is; why it is needed and how it can be used; how PM can contribute to prediction and prevention of IBD; how IBD PM can aid in prognosis and improve response to therapy; and the challenges and future directions of PM in IBD.

This first article of this series is structured on three simple concepts [what, why, and how] and addresses the definition of PM, discusses the rationale for the need of PM in IBD, and outlines the methodology required to implement PM in IBD in a correct and clinically meaningful way.

Key Words: Inflammatory bowel disease; Crohn's disease; ulcerative colitis; precision medicine; omes; omics; bioinformatics; systems biology; network medicine; interactome; biosample; artificial intelligence; deep learning; artificial neural network; drug discovery

1. What is Precision Medicine?

1.1. Introduction

Long before the modern notion of precision medicine [PM] emerged, physicians recognised that each patient is unique.[1] The first stepping stone toward PM may have been laid in 1901 when Karl Landsteiner observed that the 'serum of normal humans frequently agglutinates red blood cells of other healthy individuals'.[2] This simple observation led to the discovery of matching ABO blood groups for compatible blood transfusions. Landsteiner's landmark was mentioned by former US president Barack Obama in 2015 when he launched the National Precision Medicine Initiative [www.whitehouse.gov/precisionmedicine] to accelerate progress toward a new era of better medicine.

In the past 20 years, medical science and technology have experienced dramatic advances. However, even though we have started to understand the molecular basis of complex diseases such as cancer, medical decisions are still made primarily using conventional clinical tools.[3,4] In 2011, the US National Research Council published a report stressing the necessity for 'precision medicine' to fill the widening gap between the advances in molecular biology and its clinical applications.[5] This illustrated the necessity for development of integrated knowledge base to understand the complexities of human health and disease. We are now standing at an inflection point for a transformative leap from traditional medicine toward PM.[6]

Although the concept of PM in inflammatory bowel disease [IBD] is not new, it has the potential to dramatically benefit certain patients by customising their treatment. We have long known that patients with IBD have varying disease manifestations, disease evolution, and treatment needs. Some patients with IBD require repetitive and aggressive interventions, and others only require minimal treatment [see Verstockt B, Noor N, Marigorta U, *et al*. Results of the Seventh Scientific Workshop of ECCO: Precision medicine in IBD—disease outcome and response to therapy. *J Crohns Colitis* 2021]. It is commonly accepted that the pathogenesis of IBD includes multiple factors intertwined by highly complex molecular interactions [see Verstockt B, Noor N, Marigorta U, *et al*. Results of the Seventh Scientific Workshop of ECCO: Precision medicine in IBD—disease outcome and response to therapy. *J Crohns Colitis* 2021]. However, the incomplete understanding of IBD pathogenesis continues to pose fundamental limitations to precise and effective treatments, and current treatment paradigms are still based on broad immunosuppression rather than a customised specific therapy based on individual patient characteristics.

1.2. Definition of PM

Seeking precision in medical practice has always been considered a must, but the word PM first appeared in a publication only in 1971.[10,11] A number of other terminologies have surfaced that offer similar notions as PM, such as 'personalised medicine', 'tailored medicine', 'individualised medicine', 'high-definition medicine', and 'high-performance medicine',[11–13] with PM and 'personalised medicine' often being used interchangeably.[14] However, more important than the lexicon is what PM and comparable terminologies signify. A report of the US National Research Council Committee on a Framework for Developing a New Taxonomy of Disease states that PM is:

'*Tailoring of medical treatment to the individual characteristics of each patient to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not*.'[5]

This report emphasised the distinction between PM and personalised medicine by stating that 'personalised medicine' refers to treatments tailored toward single individuals, whereas PM seeks to identify subgroups for risk stratification that go beyond the single individual for clinical decision making. The National Institute of Health [NIH] of the USA defines PM as:

'*An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person*.'[15]

In the NIH definition, the genome and the environment [the exposome] figure prominently, but in reality several other equally important components should be included, such as the microbiome, the epigenome, the transcriptome, the proteome, the metabolome, and so on. This brings up the notion of 'omes' and 'omics' and of 'biological complexity', key topics that will be discussed later in this article. Still another publication discusses the various definitions of PM and provides a more comprehensive view by stating that:

'*PM seeks to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics*.'[11]

Despite multiple definitions, the word PM has caught the attention of society at large and has become a household name in the medical and lay narrative, but it is subjectively interpreted and used by different stakeholders. From a patient's perspective, PM is a treatment tailored to each individual, whereas for some public health agencies, PM is about genomic and cancer research.[16] Regardless of the more or less subtle differences in the various definitions of PM and how they may be perceived, what is truly important is to recognise that to achieve effective therapies, all components of a disease process must be considered and that treatments must be 'made-to-order'.

1.3. Components of PM

How many and which elements are needed for implementation of PM is open to debate, as multiple and variable components exist. One comprehensive list developed by the Committee of the Precision Medicine Platform of the University of California at San Francisco included the following: 1] basic discovery; 2] clinical discovery; 3] behavioural/social discovery; 4] digital health; 5] omics medicine; 6] computational health sciences; and 7] knowledge network [https://precisionmedicine.ucsf.edu/elements-precision-medicine]. Basic, clinical, and behavioural discovery are not novel, but they constitute the foundation on which to build new insight into the pathogenesis of a disease. Basic research investigates fundamental biological processes and generates new insights; clinical trials gather information on patient histories, habits, and outcomes; behavioural/social

discovery studies the role of behavioural, social, and environmental factors in health and disease; omics medicine collects and interprets different types of molecular information, such as the genome, microbiome, and metabolome; computational health sciences integrate vast amounts of diverse data; digital health collates and reports medical information such as electronic health records; and knowledge network integrates, interprets, and visualises collected data in ways that are clinically meaningful and reveal patterns of health and disease. Whether all the above components are essential, whether some are more important than others, whether only some are necessary depending on specific goals, or whether even more components should be included in PM is debatable. Nevertheless, it is essential to acknowledge the need for complementary sources of information to fulfil the concept of PM and implement its goals.

1.4. Omes and omics

Implicit in PM is the multiplicity, variety, and connection of disease components. It is therefore necessary to study them in an all-inclusive manner, which takes us to the notion of 'omes' and 'omics'. According to the Oxford English Dictionary, in the field of cellular and molecular biology, the suffix -ome is used to form words with the sense that 'all constituents are considered collectively'. This suffix was probably used for the first time in 1920 in the word genome to define the overall genetic material present in a cell, tissue, or living organism.[17] The term -omic followed as a suffix derived from -ome, and refers to the in-depth study of all constituents considered together to comprehend the function of combined components in a biological process.[18] For instance, proteomics is the study of the proteome, metabolomics is the study of the metabolome, and so on.

Over the past few decades, researchers and bioinformaticians have broadly used the suffixes -ome and -omic when referring to datasets extracted from a variety of biological areas with high-throughput technologies. Consequently, a large number of these datasets now exist, and a continuously updated list of all omes and omics reported in the literature is maintained by the Cambridge Health Institute and is accessible online [http://www.genomicglossaries.com/content/omes.asp]. Questions have been raised about the usefulness of so many omes in a clinical context, and criteria for appropriate omes and inappropriate omes have been proposed.[19] In reality, the value of one ome is limited if considered in isolation, since all omes inevitably interact with each other, creating the extreme biological complexity that maintains well-being in a healthy person or shifts to disease development in a sick person.

The combined study of various omes to understand how their integration results in health or disease has led to the concept of the interactome, defined as a biological network in which multiple omes are functionally integrated and lead to a particular outcome.[20] In health, the interactome has no more or less important omes; all of them are essential to maintain homeostasis. However, in disease like IBD, some omes may be temporally or mechanistically more influential and dominant than others in triggering or maintaining disease. This may include genomic variants,[21] exposome factors,[22] or microbial dysbiosis.[23] In the latter scenario, the outcome of the IBD interactome is a chronic inflammatory status that can only be controlled by intervening at the regulatory components [hubs, discussed below] of the disease network.[24]

Multiple omes must be integrated into the IBD interactome to achieve a truly comprehensive and realistic picture of its pathophysiology. An integrative worldwide collaboration on large IBD datasets has been recently proposed by the IBD Multi Omics Consortium with the aim of discovering reliable biomarkers and identifying the molecular pathways to be targeted in future drug development and intervention.[25] This demonstrates how dynamically and rapidly the whole field of omes and omics is advancing. Specifically in IBD, this is propelled by increasingly advanced technologies such as single-cell multimodal omics performed with epithelial and immune cells, which in 2019 was selected by the journal *Nature* as method of the year[26] and has already been applied in IBD.[27]

1.5. Bioinformatics, systems biology, and network medicine

By acknowledging the existence of multiple interacting components in normal and abnormal physiology, methods to comprehensively understand how they all work together are necessary. This justifies the use of cutting-edge methodologies, such as bioinformatics and systems biology.[28–30] These analytical tools permit the development of a holistic means to classify and understand diseases and to customise treatment for PM in conditions like IBD.

1.5.1. Bioinformatics

Bioinformatics is a discipline that develops advanced informatic methods to analyse and integrate large amounts of biological and clinical data.[31] The application of bioinformatics can generate alternative views of a biological response and the mechanisms of the response, and can produce information that cannot be obtained with classical analytical techniques.

1.5.2. Systems biology

Systems biology refers to the approach of investigating the interactions of all the components in a specific biological context.[32] From a medical perspective, the importance of this approach is 2-fold. First, information coming from the same patient within a defined time frame is pooled; and second, the dynamic changes rather than punctual time points to investigate any event [primary or secondary] involved in a perturbed homeostasis are analysed. Thus, what systems biology tries to do is understand which, why, and how variations occur, and where they can be targeted to restore homeostasis.[33] In addition, systems biology takes biomedical research to a higher scientific level by adopting an unbiased deductive strategy to extract significant outputs from a multitude of inputs [further explained in the 'How' section of this article], in contrast to the classical and intrinsically biased hypothesis-driven approach.[34] In this way, systems biology opens new avenues for the future of PM.[28,29,35,36]

1.5.3. Networks and network medicine

Because a bioinformatics- and systems biology-based approach to PM creates large amounts of information, the notions of 'big data' and 'high-throughput' technologies to manage them have emerged.[37] The recognition of multiple omes, the exponential growth of big data, and the creation of advanced practices have come together and have established the discipline of network medicine, ie, the development of an unbiased, comprehensive framework integrating multiomic data to understand disease mechanisms and customise drugs.[38] Network medicine is now seen as 'essential for understanding the determinants of disease expression'.[29] Various types of networks can be identified. Some examples are: molecular networks that include protein, metabolic, and transcriptomic interactions; phenotypic networks that include genetic and co-expression networks; and host-pathogen networks, such as immune cell-microbiome interactions.[39,40]

A few principles are fundamental to understand the world of networks and network medicine and to comprehend its logic.[14,41] Concisely, a network can be visualised as a web of nodes and edges; nodes represent units in the network [such as molecules, genes, and proteins], and edges [links] represent the connections between the units, whose distribution ranges from highly grouped to dispersed [Figure 1]. Some of these nodes, called hubs, are usually located centrally within the network, are highly connected to more peripherally located nodes, and control how the network operates.[42] Other nodes [bottleneck] connect and bring together distant regions of the network.[43] Areas that contain numerous clustered nodes are called modules, which typically contain controlling hubs.[44] Two main types of modules are recognised. These are functional modules, which are dense areas of nodes with similar function in the same topographical neighbourhood, and disease modules, which are aggregations of interactions that underlie a particular disease process [Figure 1].[45]

1.5.4. Application of bioinformatics and systems biology to network medicine

Network-based analytical approaches are causing a true paradigm shift in medicine,[46] as they create a workable system to apply PM to benefit patients through an alternative viewpoint of disease mechanisms and the acquisition of new capabilities to discover innovative targets for highly specific therapies.[47,48] To achieve these goals, novel analytical approaches are essential. Unfortunately, the vast majority of basic, translational, and clinical IBD investigators are not familiar with the advanced tools necessary to apply bioinformatics and systems biology to network medicine.[49,50] Thus, the solution is either to invest in demanding and time-consuming training or, more realistically, to collaborate with scientists who have the desire to apply their computational skills in IBD. How this can be achieved in practice with the goal of PM in IBD is discussed in the 'How' section of this article.

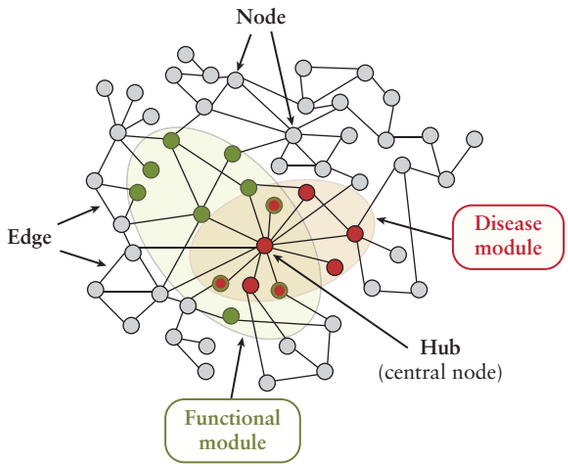


Figure 1. Basic components and structure of a biological network. A biological network is a web composed of two basic types of interconnected units linked into a whole, known as nodes and edges. A node [grey, green, and red circles] can be any biological element, such as a gene, protein, or enzyme. An edge is a link that connects and allows an interaction between two nodes. Within the network there are modules, which are clusters of closely connected nodes that modulate the function of the network and are called functional modules [light green ovals]. Some other clusters tend to be more centrally located within the network and are causatively related to a disease process and are called disease modules [light red ovals]. Some centrally located nodes within a disease module are called hubs, because they exert control over the function of the module. Importantly, hubs represent potential targets for new drugs, a possibility that requires validation in cellular or animal experimental systems.

2. Why: Why is PM Needed in IBD?

As indicated above, although conditions like IBD involve many pathogenic factors, most research is still focused on the identification of single dominant factors that may explain the initiation and persistence of the entire disease process. A good example is genomics. With the discovery of *NOD2* variants associated with ileal Crohn's disease [CD][51] and several subsequent genome-wide association studies [GWAS], genomic abnormalities began to be considered as potential 'causative' factors.[52] This assumption has been progressively undermined by the realisation: that healthy subjects carry IBD-associated genes[53]; that gene pleiotropy [defined as a single gene or variants being associated with multiple distinct phenotypes] is common in genes and single-nucleotide polymorphisms [SNP][54]; that a limited number of core genes cannot explain common diseases and biological complexity[55]; and that the role of genes must be integrated with thd roles of other pathogenic factors.[34] Another example is the gut microbiome, where a myriad of reports described a number of various abnormalities in the composition of the gut microbiota in both CD and ulcerative colitis [UC].[23] An IBD microbial signature has yet to be found, and a main reason for failing to identify unique causative microbes is the fact that the IBD-associated dysbiosis cannot be understood without considering the biological heterogeneity of the host and his/her lifestyle.[56] These and other aetiological and pathogenic factors reinforce the notion that there are no single or simple causes of IBD, and that biological complexity is at the root of CD and UC.

2.1. Biological complexity

2.1.1. What is biological complexity?

If biological complexity is an inextricable part of IBD, comprehending its meaning is mandatory. Complexity exists in all domains of life, in evolution, society, politics, economy, markets, communications, sciences, and so on. Biological complexity describes the collection of natural components that act together through interconnections such that one component's function affects those of the others.[57] Complex biological systems are non-linear, do not have fixed boundaries, vary and adapt, and are influenced by other systems.[58,59] These features explain the inherent variability of biological systems and why their outcomes are difficult to forecast.[57] Luckily, the ability to investigate biological complexity and dissect its components has increased dramatically in recent years with the development of computational technologies.[60–63]

2.1.2. What makes a biological system complex?

All biological systems are innately complex, as they are formed by numerous elements that interrelate and cluster, creating networks that ultimately mediate a function. As mentioned previously, biological networks of all types exist, including molecular, cellular, tissue, organ, systems, and organism networks. Their individual components play multiple roles that help establish physical connectivity and biological function, and together determine health or induce disease.[64]

Chronic diseases, such as IBD, are typical examples of complex biological systems and exhibit a high degree of variability. Complexity is due to the large number of interacting factors and mechanisms, and variability is due to the intrinsic heterogeneity of the affected individuals and the surrounding environment. This

results in diverse clinical presentations, changes in disease course, and unpredictable response to treatment[58,65] [see Verstockt B, Noor N, Marigorta U, *et al*. Results of the Seventh Scientific Workshop of ECCO: Precision medicine in IBD—disease outcome and response to therapy. *J Crohns Colitis* 2021]. However, it is worth noting that some degree of complexity is also present in 'simple' diseases [such as an acute infectious disease where a single agent is the known cause], as diverse biological networks must act in unison to induce resolution.

2.1.3. What is the evidence that IBD is biologically complex?

The strongest evidence comes from studies of the pathobiology of IBD.[24,66] The classical pathogenic pillars [ie, environment, genetics, microbiota, and immune system] are complex on their own and interact continuously amongst themselves. There are multiple environmental factors that overlap, change throughout life,[67–69] and exert their effect directly on the intestine or indirectly by influencing genes, microbes, or the immune system.[70] Although hundreds of genetic variants have been described in IBD, they only explain 20–25% of variance in disease liability.[71] These variants are expressed and regulated by various molecular mechanisms, with epigenetic modifications being some of the most relevant.[70,72] The gut microbiota is affected by environmental, genetic, and immune factors; its trillions of microorganisms interact with and modulate each other and influence the mucosal barrier, the intestinal and systemic immune response, and even the gut-brain axis.[73–76] Finally, the immune system is formed by a rich network of cells, cytokines, and antibodies, all of which are regulated by genes, the exposome, the microbiome, and even the central nervous system.[9,75,77,78]

Although complexity and variability are found in both CD and UC, these are two distinct non-homogeneous entities. In fact, each disease presents its own epidemiology,[79,80] pathogenic pathways,[9] clinical presentation,[81] histopathological features, course, complications,[82,83] and response to therapy,[84,85] further accentuating the overall complexity of IBD.

2.2. IBD multifactorial aetiopathology

Here we briefly consider selected aspects of some omes. The relevance of these omes is clear not only because of their biological properties but also due to their temporal participation [pre-diagnosis versus post-diagnosis], interaction with other omes, and possibility of modulation for therapeutic purposes.

2.2.1. Exposome

A large body of evidence suggests a key role of environmental factors in IBD pathogenesis. However, impact depends on the type, timing, intensity of exposure, and incremental effect of additional factors.[24,68] The influence of environmental exposures on disease course is well established for some factors but is more elusive for others.[68,86] Smoking is clearly associated with a poorer clinical course in CD but not in UC, where it can relieve symptoms,[86] drugs and stress can trigger flares,[68,86] and some dietary factors can aggravate clinical symptoms whereas others can induce remission.[87,88]

2.2.2. Genome

Genetic factors are associated with IBD susceptibility, phenotype, clinical course, and response to treatment.[66,89] Although genomic make-up is the only fixed factor in a patient, hundreds of genetic variants have been identified[21] that affect a myriad of processes, such as intestinal homeostasis, epithelial barrier function, microbial composition, autophagy, production and secretion of anti-microbial peptides, and regulation of adaptive and innate immunity [eg, *NOD2*, *ATG16L1*, *IL23-R*, *IL-12*, *JAK2*, *CARD9*, *TNFSF18*, and *IL-10*].[66,90,91]

2.2.3. Epigenome

The epigenome consists of non-genetic modifications of the genome and is responsible for modifications in gene expression. There are numerous epigenetic modifications, such as DNA methylation, histone modification, and the action of regulatory RNAs. Together, these modifications influence IBD by regulating innate and adaptive immunity, pathogen recognition, host-microbe interactions, and mucosal homeostasis and integrity.[92] Methylation is the epigenetic marker most widely studied. Methylated sites are related to IBD genetic variants,[93] and differential gene methylation exists in both CD and UC.[94,95] Moreover, some DNA methylation clusters are associated with risk of surgery, emergency hospital admission, and immunomodulatory therapy, although they are not independently predictive of outcome.[96]

2.2.4. Transcriptome, proteome, and metabolome

Transcriptomics refers to the study of gene expression as determined by mRNA sequencing, including both coding and non-coding RNAs, such as microRNAs and lncRNAs. One study revealed differing transcript expression in IBD patients responding to anti-TNF or etrolizumab,[97] whereas another study claimed that high pre-treatment expression of oncostatin M transcripts in IBD patients can identify those who will fail anti-TNF therapy.[98] IBD patients have distinct proteomic and metabolomic profiles, some of which are associated with disease activity, response to anti-TNF agents, or need of treatment scalation.[24,66] Metabolites produced by the gut microbiota also play a role in IBD, and a dynamic interplay exists between dietary and microbial metabolites in the intestine.[99]

2.2.5. Microbiome

It is generally believed that the gut microbiota is the target of an inappropriate immune response in genetically susceptible individuals, and that this event is central in IBD pathogenesis.[9,100] Although this assumption remains to be proven, the role of the microbiome is indisputable. The microbiome has many functions essential to health, such as immune system development, establishing tolerance, absorbing and metabolising nutrients, and even epigenetic modifications.[101–104] A large body of evidence shows that IBD is associated with quantitative and qualitative alterations of the gut microbiota, such as decreased diversity, reduced proportions of Firmicutes, and increased proportions of Proteobacteria and Actinobacteria.[73] A link between the microbiome, the immune system, and chronic diseases like IBD has been proposed,[105] and numerous reports have linked IBD microbiome abnormalities with disease phenotype, disease course, and response to treatment. However, whether these abnormalities are the cause or the consequence of IBD is still an open question.

2.3. IBD patient heterogeneity

The term 'heterogeneity' refers to fundamental characteristics that result in variability or diversity.[106] In medicine, heterogeneity stratifies patient groups based on genetic background, clinical phenotype, or environmental traits. This creates clinical variations and explains differences in response to treatments.Although IBD heterogeneity exists at multiple levels, this section will focus only on the contribution of genetics and microbial diversity to patient heterogeneity.

GWAS have identified over 200 risk loci in IBD,[21,107–109] indicating an extraordinary level of genetic diversity. IBD-associated variants

can be both unique or shared between CD and UC, and many variants overlap with those of other immune-mediated inflammatory diseases.[110] Variants implicated in innate immunity, such as *NOD2*, *Atg16L1*, and *IRGM*, are associated with an increased risk of CD, particularly ileal CD, but not UC.[111–116] Moreover, associations of IBD genes are limited to certain groups such as Caucasian populations, but not to non-Caucasian populations.[117]

There are well-known abnormalities of the microbiota in CD and UC, and some studies have reported differences in gut microbial composition between CD and UC.[118,119] A recent report investigated the gut microbiota in IBD and control subjects in considerable detail, and revealed that the microbiota is not only highly variable but also unstable during disease evolution.[23] Additional studies also found specific variations in the IBD virome and mycobiome.[120,121] This lack of consistency is most likely due to the influence of genetic factors and the host response on the gut microbiome,[56,104,122] which reinforces the notion of heterogeneity in IBD.

2.4. IBD clinical variability

The great clinical variability during IBD evolution has long been recognised and has been objectively documented by the IBSEN Study Group [https://www.med.uio.no/klinmed/english/research/projects/ibsen-inflammatory-bowel-disease/]. Once a diagnosis of IBD is established, the patient should be stratified into the appropriate subgroup. This is particularly important for those with an unfavourable clinical course, as the therapeutic approach should be adjusted accordingly. Although clinical parameters, environmental factors, and biomarkers have been proposed to predict the variable clinical course of IBD, none of these is reliable enough to dictate management decisions.[123] The same is true for selected clinical features, such as extensive lesions, strictures, or fistulas that are usually associated with unfavourable disease course in both UC and CD.

Some studies have suggested that variation in clinical phenotype can be explained by investigating genotype-phenotype associations. In CD, a correlation between young age, complicated disease course, and *NOD2* polymorphism has been described.[124,125] The risk allele rs2241880 of *ATG16L1* is associated with perianal disease.[126]

In UC, *HLA-DRB1* alleles are associated with development of complicated disease. In particular, the *HLA-DRB1*0103* allele is associated with the development of pancolitis, extraintestinal manifestations, and an increased risk of surgery.[127] A meta-analysis revealed that development of colorectal cancer in IBD was associated with a polymorphism of TNF-α.[128]

Distinct treatment responses are also linked to IBD genetics. Genotyping of the thiopurine S-methyltransferase [TPMT] gene has long been used to determine the correct dosage of thiopurines. Variations in the *NUDT15* gene have been identified as a major risk factor for thiopurine-induced bone-marrow suppression.[129] Additional studies suggest a correlation between gene variants and response to certain medications. In CD, the GG genotype of *Atg16L1* may influence response to steroids, immunosuppressants, and biologic treatments,[130] and in UC the *IL-23R* genotype may affect response to infliximab.[131]

Microbiome patterns have also been investigated as a possible cause for IBD variability. A paediatric study investigated the microbiome to distinguish IBD from controls and distinguish CD from UC.[132]

It is clear that clinical, biochemical, genetic, and microbial parameters exhibit a daunting degree of variability among IBD patients. As current approaches are inadequate to address this complexity, alternative and more precise approaches are necessary to identify patient subgroups and their respective therapeutic needs.

2.5. IBD temporal variability

IBD is a spectrum of disease phenotypes, and it is possible to observe a shift from one diagnosis to another in a proportion of patients. As high as 10% of patients initially diagnosed with UC might have their diagnosis refuted or changed to CD in the first 5 years,[133] whereas CD is subsequently re-classified as UC in 5% of cases during the first year.[134] Once a diagnosis of either CD or UC has been established, a dynamic course and an unpredictable disease evolution are to be expected. Two major clinical characteristics can change during follow-up. Whereas disease location is relatively stable, disease behaviour is more prone to changes; both can be detected and monitored using the Montreal Classification for CD and UC[81] and the Mayo score for UC severity.[135]

A typical evolution for UC is extension from proctitis or left-sided colitis to pancolitis, although anatomical regression can also occur. A recent epidemiological study during the first 5 years after UC diagnosis revealed that 21% of patients with limited colitis experienced progression to extensive colitis, whereas regression was observed in 27% of pancolitis cases.[80] In CD, progressive changes in the location of affected areas and in behaviour from inflammatory towards steno-penetrating phenotypes are almost the norm, together with an increased risk of complications and operations.[136,137] A prospective inception cohort study, conducted during the first 5 years after diagnosis of CD, reported progression in disease behaviour to penetrating or stricturing disease in 14% of non-stricturing non-penetrating cases and in disease location in 12% of patients.[79]

Nonetheless, approximately 80% of IBD patients maintain stable clinical features, at least in the first few years after diagnosis. Therefore, the logical question is what is responsible for IBD clinical stability or variability over time. Tentative answers for this crucial issue have again been sought in traditional pathogenic factors, such as the genome, exposome, and microbiome. For example, at the genetic level, *NOD2* variants and other gene polymorphisms are associated with a more aggressive course of CD,[138] although the loci contributing to prognosis and disease behaviour may be distinct from CD susceptibility genes.[139] Regarding environmental risk factors, smoking is consistently associated with CD complications,[140] whereas higher rates of UC flares after smoking cessation have recently been contested.[141,142] The beneficial role of appendectomy in patients with active UC is controversial, but might affect the clinical course.[143,144] Diet is another fundamental variable when evaluating IBD progression, as processed foods have been reported to perpetuate intestinal inflammation.[145–147] On the other hand, enteral nutrition and elimination diets have demonstrated a beneficial effect on the natural history of the disease.[87,148–151] Finally, the microbiome and its modulation by the exposome also seem to be involved in altering the status of IBD and the evolution towards complications.[152,153]

Whereas the observations above may be correct, they are solely based on clinical and laboratory data and provide no insights into the mechanisms responsible for the temporal variability of IBD or what interventions are necessary to prevent clinical progression and its complications.

3. How: How Is PM Applied to IBD?

The arguments presented on ‘what is PM’ and ‘why is PM needed in IBD’ should have convinced the reader that PM is not simply

an innovation, but is an imperative alternative to the challenges of IBD that remain unsolved after decades of applying traditional research methods. Innovation always perturbs the convenience of the status quo because it demands extra effort to learn unfamiliar topics. However, the obligation to do the best for patients should supersede any inconvenience and create the resolve needed to be at the cutting edge of the IBD field. The goal of this section is to describe and explain the tools and methods for PM implementation and convince the reader that PM can ultimately solve the challenges of IBD.

3.1. IBD patient biomaterials

3.1.1. What are biomaterials and biosamples?

Long before the advent of PM, research in IBD was conducted by utilizing physical resources obtained directly from patients with CD or UC [ie, biomaterials and biosamples]. The term 'biomaterial' refers to a discrete physical item composed of biological material and containing information that can be extracted and used for biomedical purposes, and the term 'biosample' refers to a representative portion of the biomaterial to be used for experimental purposes. Biosamples derived from patients and healthy volunteers are essential in the development of new ways to understand, diagnose, prevent, or treat conditions like IBD. The extracted information is critical to create a context of tangible data, as biosamples establish a bridge between clinical and laboratory settings. This enables investigators to discover new biological perspectives and link them to clinical aspects of the disease.[154]

3.1.2. What types of biomaterials are needed for IBD PM?

When compared with investigators of other chronic complex diseases, the IBD investigator is fortunate to have the widest possible variety of biomaterials for clinical, translational, and molecular studies. These include intestinal tissue, blood, serum, plasma, urine, stool, and other bodily fluids or components [Table 1].[155]

The initial step for implementation of PM in IBD is to have access to well-defined and carefully phenotyped CD and UC patient populations as a source for the biosamples. These biosamples can be processed immediately or stored frozen in a biobank, depending on the timing and type of subsequent use. Whereas organising an IBD biobank is a complex and expensive endeavour, processing, labelling, and storage technologies are readily available.[156,157] When properly used, these resources not only make precious study items accessible to individual investigators and the IBD community at large, but also promote clinical and scientific collaborations and help produce high-quality publications.[156,157] Together with bioinformatics and electronic medical records, biobanking creates the ideal conditions for executing top-quality PM.[158,159]

A fundamental consideration is to obtain biomaterials from different sites of the same organ of the same patient at the same time. For example, this could be endoscopic biopsies from different bowel segments of a given IBD patient in a particular clinical situation. This is indispensable, considering host heterogeneity and the biological and temporal variations that result from the disease process. Anatomical location is important in disease development and should also be considered when evaluating diagnosis, treatment, and prognosis.[160]

3.1.3. How many types of biomaterials are necessary for IBD PM?

Standardising biosample procurement using collection kits is a good starting point for specimen and data collection. The most common types of biomaterials needed for IBD PM are blood, endoscopic biopsies, and stool.[161] Many trials performed in leading academic centres already have sufficient infrastructure for processing biosample collection. Blood and biopsy samples can be used to perform genomic, epigenomic, transcriptomic, metabolomic, and proteomic analyses, and stool samples can be used for microbiome and metabolomic analyses. Thus, these biomaterials are appropriate to study the most relevant omes needed for IBD PM, with the help of bioinformatics support.[156,157]

3.1.4. What types of patients should biosamples come from?

Biosamples should be obtained from a variety of CD and UC patient cohorts, including inception cohorts, longitudinal prospective cohorts, ethnic cohorts, geosocial cohorts, and paediatric and adult cohorts. This builds into the biosample the biological effect of a multitude of factors intrinsic to the trigger, evolution, behaviour, and outcome of IBD, all of which are critical to understand disease mechanisms. Considering that IBD is a typical chronic disease, collection of baseline and prospective longitudinal biosamples is essential. Ideally, biosamples should be collected from at-risk subjects, at the time of first diagnosis and before treatment, and at specific time points after IBD diagnosis. Examples of longitudinal-specific time points include during flare-ups and remissions, during complications [drug-related adverse events, extraintestinal manifestations, dysplasia or cancer, surgery], and during response to treatment [primary full response, partial response, primary or secondary loss of response].[9]

3.1.5. How many times and how often should biosamples be procured?

The results from biosamples obtained at early stages of IBD development can provide unique insights on disease evolution.[162] Thus, frequent biosampling in early IBD phases [ie, in the first year from diagnosis] may be more valuable than biosampling in chronic phases [ie, after many years] when disease burden has caused non-specific secondary and irreversible pathobiological changes. The natural history of IBD evolves for years and therefore biosampling should be a long-term process. However, the logistics of the procurement process, the time allowed for the search, the relative costs, and the resources available for long-term procurement should also be considered.[163]

3.2. Number and types of omes needed for IBD PM

The crucial importance of collecting many different types of data from diverse sources and integrating them into a single comprehensive view of IBD pathobiology [ie, the IBD interactome][24,164] has been repeatedly emphasised in the preceding sections of this article. Thus, the value of studying IBD from an 'omic perspective' is evident, as opposed to perpetuating IBD research that is narrowly focused on single factors, such as one cytokine, one receptor, one signalling pathway, or one microbe at a single time. In the following sections, a qualitative and quantitative view of how to perform IBD research for the purpose of achieving IBD PM will be presented through an omic perspective.

3.2.1. How many omes are necessary for IBD PM?

Initial GWAS investigated the genome of IBD patients and identified numerous loci associated with CD and UC.[165] This was followed by additional studies that examined the role of epigenomics, transcriptomics, and microbiomics in IBD pathobiology and their potential usefulness for biomarker development.[94,166,167] More

Table 1. Sources, types of biomaterials available in inflammatory bowel disease [IBD], and their potential use.

Source of biomaterials	Types of biomaterials [at diagnosis and during follow-up]	Use in all patients [at diagnosis and during follow-up]	Personalised use in refractory patients
Intestinal tissue			
Endoscopic mucosal biopsies from involved and uninvolved segments of the gastrointestinal tract [oesophagus, stomach, duodenum, jejunum, ileum, large bowel]	Immune cells Epithelial cells Endothelial cells Mesenchymal cells Fibrotic tissue Other cells of specific interest	X	X
Full-thickness sampling from the gastrointestinal tract during major surgery	Intestinal tissue Epiploic tissue Omentum Other adipose tissue Fibrotic tissue Venous/arterial vessels Lymphatic vessels Lymph nodes	X	X
Sampling from adjacent areas during minor surgery	Fistulous tissue Perianal skin tags	X	X
Biopsies from sites or organs other not affected by IBD [ie, skin]		X	X
Blood			
Cells and soluble products of immunity and inflammation	Serum Plasma Circulating B and T cells Other innate and adaptive immune cells Other cells [ie, erythrocytes, platelets]	X	X
Other fluids			
	Saliva Urine Septic collections [abscess] Other fluids [ie, ascetic, synovial, pleural, pericardial]	X	X
Gas			
	Intestinal gas from upper and lower intestinal tract		X
Stools			
	Extruded stools and ileostomy stool collection	X	X
Endoscopic suction materials			
Endocytoscopy and molecular endoscopy	Gastric, duodenal, ileal, and colonic suction materials for cytology and culture		X
Brush/smear materials			
	Buccal smear Pap smear Targeted segment or organ brushing during endoscopy		X
Cell cultures/organoids			
	Biopsies, tissues, or cells from involved and uninvolved segments of the gastrointestinal tract		X

recently, studies that performed more than one IBD ome analysis have been published. These combined primarily SNP array data [genome], RNA sequencing data [transcriptome], and enrichment or loss of bacterial species [microbiome].[168–171]

There is no correct or incorrect answer to the question of how many omes are necessary for IBD PM and how to predict and optimise the response to IBD therapeutics. To determine the appropriate number of omes, it is essential to consider first what IBD biomaterials are available, the cost of performing multiple omics and, most importantly, to examine what is the aim of the study. For example, is the aim to identify a blood biomarker that correlates with response to an IBD medication? Is the aim to identify novel genes and factors involved in IBD pathogenesis? For these two specific questions, different types and different numbers of omes are required.

Knowledge and experience accumulated from previous and ongoing efforts to study cancer PM can be used to choose of how many omes are needed to reach predictive value in a complex disease such as IBD.[172–175] Valuable information has been gained from cancer PM studies: a] two to four omes are sufficient to capture the variation and factors involved in the pathogenesis of different cancer types;

b] integration of two to four omes can be used to stratify cancer patients into subtypes and contribute to the development of cancer precision therapeutics; c] combination of more omes contributes to creating a comprehensive picture of the molecular mechanisms involved in cancer pathobiology [eg, if a gene harbouring a disease SNP is deregulated at both the transcriptional and the protein levels, this particular gene most likely has functional significance in disease pathogenesis and is not the translation of a random or secondary event]; and d] addition of more omes increases the power of statistical analysis and decreases the size of the patient group to be analysed. Although IBD is distinct from and a more heterogeneous disease than cancer, based on several cancer PM initiatives two to five omes should be sufficient to stratify IBD patients and match their subtypes with specific IBD therapeutics.

3.2.2. What types of omes are necessary for IBD PM?

The next step is to examine which particular omes are necessary and appropriate for IBD PM. It is nearly impossible to design the 'perfect IBD omics study' and to analyse most of the omes from biomaterials derived from the same IBD patient group consisting of 2000–3000 individuals. As discussed above, whereas the nature and the goal of the study should be the main determinants for the selection of the omes, the cost and availability of IBD biomaterials should also be considered. High-throughput studies have generated solid evidence regarding the involvement of the genome, epigenome, transcriptome, proteome, metabolome, and microbiome in IBD.[23,176–179] A large number of studies has identified over 240 IBD-associated genetic loci in thousands of IBD patients,[107] and thus genomic analysis must be included in IBD PM. However, it is not necessary to perform expensive whole-genome sequencing analyses; a focused immunoSNP array analysis may be sufficient.[180] There are also multiple publications that have implicated the role of transcriptomic alterations in IBD.[181–184] Changes in proteome can be predicted by changes in gene expression, and there are several computational tools that can integrate the transcriptome with other omes and correlate with drug responses.[185] A large number of studies have described alterations in the IBD gut microbiota and the contribution of dysbiosis to IBD pathogenesis through interaction with immune and other cell types.[186–189] Thus, in practical terms, transcriptomics and microbiomics should be able to capture and predict alterations in the proteome and metabolome. Therefore, the omes necessary to start a comprehensive IBD PM study can be limited to the genome, transcriptome and microbiome, at least initially.

A separate parameter to consider is the intricate biological interrelationship among the different IBD omes. Gene mutations and SNPs [genome] affect gene expression [transcriptome], which regulates the levels of intracellular and secreted proteins [proteome] and metabolites [metabolome], and bacteria [microbiome] secrete metabolites [microbial metabolome] which affect signalling pathways in immune [immunome] and other cell host cell types.[190,191] Thus, for example, the genome and transcriptome are more closely related to each other than the genome and proteome or microbiome are. Based on this rationale, biologically 'logical' omes should be first considered for IBD PM, especially if the aim is to understand the molecular mechanisms of IBD pathobiology and to identify novel drug targets.

3.2.3. How often should omes be collected for IBD PM?

The answer to this question again depends on the nature of the study. IBD is not a static disease predominantly driven by genetic alterations, such as cancer. Therefore, capturing IBD omes just once is inadequate. A prospective longitudinal analysis of various IBD biomaterials, and performing omes analysis in the same IBD patient during disease evolution, would provide the most comprehensive IBD map. Again, it is also important to consider the cost and the logistics of the study. For example, if the aim is to identify genes and biomarkers that correlate with clinical activity, biomaterials should be collected when the patient has active disease and again when the disease is in remission. If the aim of the study is to identify genes and biomarkers that correlate with drug response, then omes should be collected before initiation of treatment and again at 8–12 weeks if the drug is evaluated for induction therapy or 48–52 weeks if the drug is examined for maintenance therapy.

3.2.4. Should all omes always be collected at all times for IBD PM?

Ideally it would be optimal to collect all omes at all times, but this is not practically feasible. To perform a longitudinal study in IBD patients and collect biomaterials at multiple times is only feasible if the study collects non-invasive biomaterials, primarily stool samples. The microbiome is one of the few omes that can be evaluated at any time, and blood samples should also be collected most of the time. This would allow genomic, transcriptomic, and proteomic studies to be performed frequently and longitudinally. On the other hand, there are obvious limitations to the frequent collection of IBD tissue biopsies. Currently, there are innovative technologies that accurately quantify proteins and metabolites in saliva and blood samples,[192–195] but these technologies must be tested in IBD biomaterials before they can be recommended for IBD longitudinal studies.

3.3. Integrating IBD omes, identifying IBD patterns, and IBD patient subtyping

3.3.1. Which tools are available to identify distinct IBD patterns?

The past decade has seen an explosion of novel computational tools that can analyse primarily genomic, transcriptomic, and microbiome omic datasets. On the other hand, there are still relatively few tools that can analyse epigenomic and proteomic data. Thus, the computational tools needed to fully analyse all relevant omes are still a work in progress. Table 2 provides an overview of currently available computational tools applicable to IBD.

Integrated analysis of different omes is indispensable for identifying patterns in any biological setting. This is also true for grouping IBD patients into molecular—rather than clinical—subtypes, including the use of clinicopathological parameters derived from electronic medical records. In this way, the integrated IBD omes and associated patterns would have clinical significance and could correlate with clinical outcome predictions. Currently, it is increasingly clear to the IBD community that 'labelling' an IBD patient as a UC or a CD patient is no longer a satisfactory categorisation. There is accumulating evidence that the anatomical location of inflammation is a key determinant of disease pathobiology and not the UC or CD 'clinical label'.[196] Thus, patterns that can subclassify IBD patients at a molecular level are critical to develop therapeutics that target the underlying disease process rather than the clinical diagnosis. By doing so, the resulting therapeutics will not only be more specific but also less toxic for each IBD subtype, a concept that is widely and successfully applied in the oncology field.[197–200]

Regrettably, all the omics data integration tools have thus far been developed for oncology patient applications and not for chronic inflammatory diseases, like IBD. Thus, a prerequisite in developing tools that are specifically applicable to IBD is the generation of IBD omics datasets to serve as training sets for the current computational tools. A computational algorithm that could be applied to identify IBD patterns is PARADIGM, a pathway recognition algorithm.[201] Furthermore, Integrative Bayesian Analysis of Genomic Data [iBAG] is an algorithm that provides a framework to recognise the key factors associated with IBD clinical outcomes.[202] Another computational tool is iCluster, which is based on a joint latent variable model able to simultaneously integrate IBD multiomics datasets and generate a single integrated cluster.[203] iCluster+ is a newer version of iCluster that can perform complex disease pattern analysis, and has been used extensively by the NIH TCGA consortia and successfully identified novel cancer patient molecular subtypes.[204] Another tool called Tied Diffusion Through Interacting Events [TieDIE] allows searching for statistically significant interconnections between genotype perturbations and molecular network shifts.[205]

3.3.2. Artificial intelligence-based computational tools for IBD PM

The ability of an investigator to examine millions of datapoints, correlate them with IBD clinical parameters, and connect them with the current literature is grossly inadequate.[206] Artificial intelligence [AI] can facilitate the development of computational systems able to perform tasks similar to, complementary to, and far more advanced than those achievable by human intelligence. The computational revolution in recent years has provided us with a plethora of AI tools that can unravel complex problems related to different aspects of human life [Table 2]. These tools have already been applied in the biomedical field and have contributed to more accurate and efficient diagnosis, image analysis, classifications, and predictions [Torres J, Halfvarson J, Rodríguez-Lago I, *et al*. Results of the Seventh Scientific Workshop of ECCO: Precision medicine in IBD—prediction and prevention of inflammatory bowel disease. *J Crohns Colitis* 2021; Verstockt B, Noor N, Marigorta U, *et al*. Results of the Seventh Scientific Workshop of ECCO: Precision medicine in IBD—disease outcome and response to therapy. *J Crohns Colitis* 2021].[63,207–212]

Machine learning is a branch of AI where computer algorithms improve automatically through experience,[213] and machine-learning algorithms can be used to integrate multiomics IBD datasets for PM studies. The process of 'IBD pattern recognition' takes IBD omics datasets and extracts patterns based on clinical, molecular, and microbial factors and leads to the identification of IBD patient subtypes. This pattern-recognition analysis in IBD can be performed with an 'artificial neural network' analysis.[214] The term 'neural network' is derived from the fact that it mimics the human brain neuronal networks and uses stimuli as inputs and converts them into actions [outputs] [Figure 2].

The structure of an IBD neural network consists of three major layers.[13,85,215] The first is the input layer, which is responsible for receiving the individual IBD omics datasets, such as the IBD genome, transcriptome, or microbiome. Next, there are the hidden layers that are not visible [dark box] and perform all the complex calculations and combinations, with the number of the hidden layers depending on the complexity of the omics datasets and the task. Finally, the output layer receives signals from the hidden layers and regresses the information, providing a final result [Figure 3].[216] To create and optimise an IBD neural network analysis, it is essential to first generate a high-quality IBD omics dataset to be used for machine learning training. This dataset will contribute to the identification of the appropriate architecture of the IBD interactome and identify the various weights of each node and parameter in the disease network.

Recently, an IBD study aimed to classify more than 18 000 CD patients based on their Immunochip SNP array analysis and revealed that neural network analysis was superior to other methods, such as logistic regression and decision tree analysis.[217] It is essential to note that, in order to perform a clinically relevant IBD neural network analysis, all ome datasets must derive from the same IBD patients. A recent study used a deep neural network approach and identified specific microRNAs and five clinical parameters that predict drug response in patients with severe UC.[218] Another study that integrated a high-throughput inflammatory cellular screen with human IBD patient data identified miR-124 as a central regulator of an UC inflammatory network.[219] This led to development of a small molecule that activates miR-124 in moderate-to-severe UC patients which is currently in a phase II clinical trial [https://clinicaltrials.gov/ct2/show/NCT04023396].

The computational tools and methodologies described above represent just a few examples of the exciting technologies that can be used for IBD PM initiatives. There are many other tools under development than can identify patterns based on multiomics disease data. To do so, is essential that IBD investigators do not pick computational tools at random, but carefully evaluate which tool is 'IBD suitable' and appropriate for the specific project. These initial AI-powered IBD studies and AI-based tools expose the power of omic data integration and machine-learning approaches for implementation of PM in IBD.

3.4. Tools for omes integration into IBD networks

3.4.1. Tools for network construction, visualisation, and hub identification

A strategic aim in IBD PM is to identify the molecular drivers of inflammation that initiate disease and define patient subtypes [Torres J, Halfvarson J, Rodríguez-Lago I, *et al*. Results of the Seventh Scientific Workshop of ECCO: Precision medicine in IBD—prediction and prevention of inflammatory bowel disease. *J Crohns Colitis* 2021; Verstockt B, Noor N, Marigorta U, *et al*. Results of the Seventh Scientific Workshop of ECCO: Precision medicine in IBD—disease outcome and response to therapy. *J Crohns Colitis* 2021]. Thus, a network and interactome analysis must be performed to identify the central regulators [hubs] that drive pathogenesis in any particular subtype [Table 2]. Cytoscape is one of the most widely used computational tools for omics data integration and network build-up, and enables omic data import, export, integration, and construction of the IBD interactome.[220] Importantly, Cytoscape can also be used to visualise and analyse IBD network graphs organised as nodes and edges.

A key feature of the Cytoscape software architecture is the acceptability of plug-ins [software components that add specific features to an existing computer program] for specialised needs. For example, the Algorithm for the Reconstruction of Accurate Cellular Networks [ARACNE] algorithm uses an information theoretical approach to eliminate the vast majority of indirect interactions typically inferred by pairwise analysis.[221] Omics Visualizer is another Cytoscape plug-in that allows users to import data

Table 2. Common computational tools available for disease pattern identification, patient subtyping, network construction and visualization, hub identification, omics-therapeutics linkage, and drug toxicity prediction.

Name	Function of software	Weblink	Refs
PARADIGM	Multiomics data integration	https://sbenz.github.io/Paradigm/	201
iBAG	Identify genes linked to clinical outcomes	http://odin.mdacc.tmc.edu/~vbaladan	202
iCluster	Identification of disease molecular subtypes	https://cran.r-project.org/web/packages/iCluster/index.html	203
iCluster+	Complex disease pattern analysis	https://www.bioconductor.org/packages/release/bioc/html/iClusterPlus.html	204
TieDIE	Gene-protein interaction networks	https://github.com/epaull/TieDIE	205
Cytoscape	Visualisation of omics networks	http://www.cytoscape.org/	220
ARACNE	Cellular networks builder	http://apps.cytoscape.org/apps/aracne	221
Omics Visualizer	Gene network visualisation	http://apps.cytoscape.org/apps/omicsvisualizer	222
BiNGO	Gene ontology of biological networks	http://www.psb.ugent.be/cbd/papers/BiNGO/Home.html	223
GenePro	Visualisation of disease interactome	http://wodaklab.org/genepro/	224
Cytocom	Visualisation of comorbidity networks	http://www.cl.cam.ac.uk/~mam211/	225
CHAT	Identification of network hubs	http://apps.cytoscape.org/apps/chat	226
cytoHubba	Identification of hubs and subnetworks	http://apps.cytoscape.org/apps/cytohubba	227
DyNet	Most "rewired" nodes across different inflammatory bowel disease network states	http://apps.cytoscape.org/apps/dynet	228
Connectivity Map	Identification of drug-gene signature interactions	https://www.broadinstitute.org/cmap/	185
LINCS	Integrated network-based cellular signatures	http://www.lincsproject.org/	248
CellMiner	Chemical-genetic profiling	https://discover.nci.nih.gov/cellminer/	249
ISA	Associations between a drug and gene signature	https://www2.unil.ch/cbg/index.php?title=ISA	250
iFad	Pathway-based drug discovery	http://bioinformatics.oxfordjournals.org/content/28/14/1911.long	251
DrugMatrix	Drug-gene expression datasets	https://norecopa.no/3r-guide/drugmatrix	252
TG-GATEs	Gene expression: toxicology datasets	http://toxico.nibio.go.jp/english/index.html	253
ConsensusPathDB	Meta-database for molecular interactions	http://cpdb.molgen.mpg.de/	254
ToxDB	Pathway toxogenomics data	http://toxdb.molgen.mpg.de/	256

tables with multiple rows referring to the same network node and to visualise such data in the networks.[222] BiNGO is a Cytoscape plug-in to assess over-representation of gene ontology categories in IBD biology networks.[223] GenePro is a another Cytoscape application that can consent advanced visualisation and analysis of the IBD interactome.[224]

An important aspect of IBD and many other complex diseases is the presence of comorbidities. Cytocom Cytoscape allows search, exploration, analysis, and visualisation of comorbidity networks.[225] It represents disease-disease associations in terms of bipartite graphs, and provides International Classification of Diseases, Ninth Revision [ICD9]-centric and disease name-centric views of clinical information.

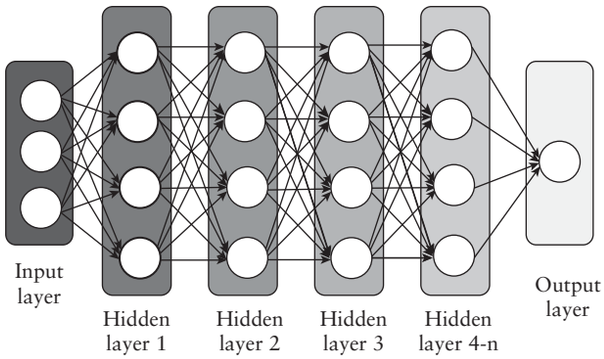


Figure 2. Basic structure of an artificial neural network. An artificial neural network consists of an input layer, an output layer, and several hidden layers between them. The input layer is responsible for receiving information, such as clinical, microbial, genetic, transcriptomic, metabolomic, or other data. The hidden layers are always between the input and output layers, are not visible to external systems, and their number depends on the complexity of the biological process being studied [eg, inflammatory bowel disease] and the number of omes included in the network analysis.

3.4.2. Methods for hub identification in IBD networks

In addition to the identification of the central regulators of the IBD interactome, a key goal in IBD PM and network analysis is to discover the individual drivers to be therapeutically targeted [Table 2]. How can these central hubs of the IBD interactome be identified?

Highly connected nodes [hubs] are topologically important to the structure of any interactome, including the IBD interactome. It is important to note that the relative importance of a hub may change depending on the biological context and the disease state. The Contextual Hub Analysis Tool [CHAT] allows construction and visualisation of an IBD network of interactions, integrates contextual information, and identifies the IBD hub nodes that are more highly connected to contextual nodes.[226] The cytoHubba algorithm can identify the key hubs and subnetworks in a given IBD network by using several topological algorithms.[227] Specifically, cytoHubba has the ability to identify hubs in an interactome through topological algorithms, such as Maximum Neighbourhood Component [MNC] and centralities based on shortest paths, such as Bottleneck [BN] and EcCentricity.

The unpredictable nature of IBD and the ever-changing interaction of its omes represent major challenges in creating a dynamic IBD interactome that adjusts continuously during the timeline of disease development, flares, remissions, and treatments. DyNet is a Cytoscape application that allows analysis of large multistate dynamic molecular interaction networks and enables users to identify the most 'rewired' nodes across different IBD network states.[228] The DyNet algorithm could enable IBD investigators to move from static to dynamic IBD network analysis, uncovering new insights into how the networks forming the IBD interactome are physically rewired in response to different clinicopathological circumstances.

3.5. Linking IBD networks to PM therapeutics

Since the first report of the beneficial effect of anti-TNF monoclonal antibodies in CD,[229] the number of therapeutic agents for IBD has

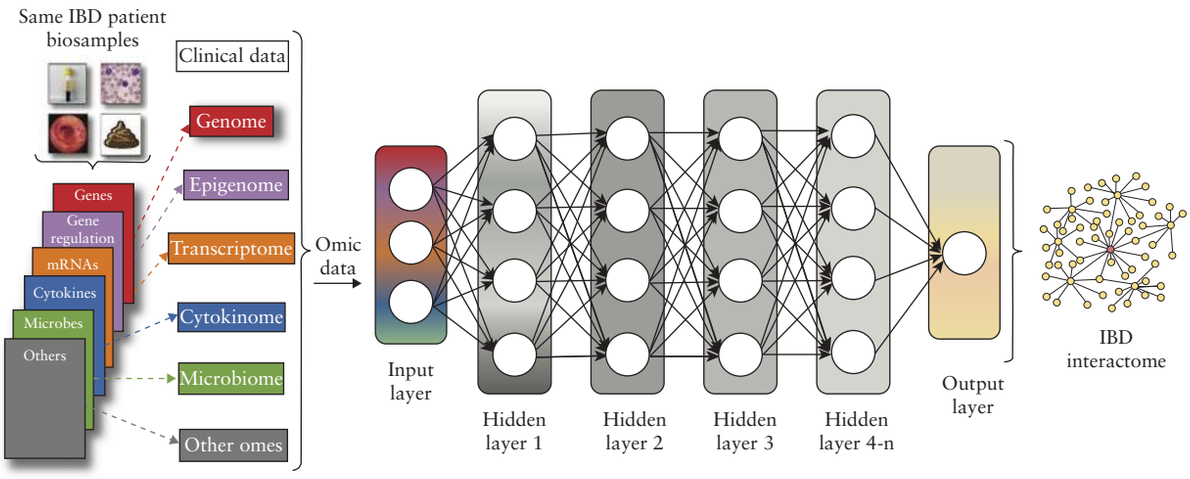


Figure 3. Graphic representation of the data entered in the input layer of an artificial neural network and the data generated by the output layer of the same network. A variety of omics data, resulting from the analysis of multiple omes from individual IBD patient biosamples, is entered in the input layer and is processed by the hidden layers, whose number varies depending on the complexity of the data. Once processing is complete, the output layer delivers the information contained in the omic data, represented in this example by a biological network [ie, the IBD interactome that underlies the pathobiology of the donor patients]. IBD, inflammatory bowel disease.

increased exponentially. Today, clinicians must carefully select the best drugs for their patients from a large therapeutic armamentarium.[230] Despite this progress, the individual effectiveness of old and new agents has not proportionally increased. Even in the most recent IBD clinical trials, clinical response, clinical remission, and mucosal healing [endoscopic remission] remain between 20–50%, regardless of the type of agent administered.[231–237] Perhaps these results should not come as a surprise if we consider that most new agents still target one molecule or one pathway at a single time point of the extremely complex, multifactorial, and dynamic inflammatory process controlled by an intricate IBD interactome. Although not yet experimentally proven, single agents probably interfere with some peripheral components of the IBD interactome, which is insufficient to disrupt the disease network[238] and causes only temporary destabilisation that manifests as transient or partial clinical improvement. In contrast, if drugs are developed to specifically target hubs of disease modules that are centrally located within the IBD interactome, the chances of disrupting the disease network substantially increases and should result in far greater and more durable clinical benefit.[239,240] In fact, there is evidence that the drug therapeutic effect resides in a small network of disease-associated genes,[241] which allows investigation of drug-disease links for drug repositioning [see below] and implementation of PM.

3.5.1. Linking IBD omics signatures to PM therapeutics

Several computational tools have been developed that allow prediction of the mechanism of action of a new drug or the potential use of an approved drug for another indication, a process called 'drug repositioning' [Table 2].[242–245]

Connectivity Map [CMap] is a comprehensive catalogue of cellular signatures obtained as transcriptional responses to chemical, genetic, and disease perturbations. To date, CMap has generated a library containing over 1.5 million gene-expression profiles from approximately 5000 small-molecule compounds and 3000 genetic reagents tested in multiple cell types. With this tool, researchers can compare gene-expression profiles with those in the library. Perturbations that elicit highly similar or highly dissimilar expression signatures are termed 'connected', and their transcriptional profiles suggest that such perturbations confer a corresponding biological effect.[185,246,247] The platform can be used as the first step in the drug discovery process to analyse signalling pathways and to uncover structure-function relationships. Similar to CMap, the Library of Integrated Network-based Cellular Signatures [LINCS] Consortium includes datasets that consist of assay results from different types of tissues and cells treated with bioactive small molecules, ligands such as growth factors and cytokines, or genetic perturbations.[248]

CellMiner is a web-based suite of bioinformatics tools designed to perform chemical-genetic profiling based on drug and gene activity. Designed for cancer therapeutics and based on data from a particular cancer cell line panel [NCI-60], CellMiner allows discovery of mechanisms of action of uncharacterised and structurally similar compounds.[249] Although this tool could contribute to the identification of novel IBD therapeutics, the IBD community should also consider developing IBD-specific in vitro or ex vivo cellular panels to perform IBD chemical-molecular profiling studies.

Additional computational tools to assess the associations between a drug and gene signature include the Iterative Signature Algorithm [ISA][250] and the integrative Factor Analysis for Drug-pathway association inference [iFad], which compares gene expression with drug sensitivity profiles to discover drug-pathway associations.[251]

3.5.2. Computational tools to predict drug toxicity and safety profiles

Toxicity is a measure of any undesirable or adverse effect of a new or old therapeutic agent. Although animal models are routinely used for extensive and detailed toxicology studies, novel computational tools have recently been developed that can complement traditional in vivo studies. Computational toxicology is a type of toxicity assessment that uses mathematical resources, such as algorithms, to model, simulate, and predict drug toxicities. Toxicity effects are not uncommon with current IBD therapeutics, and therefore it is essential to perform an in silico toxicology analysis during the development of any new IBD therapeutic [Table 2].

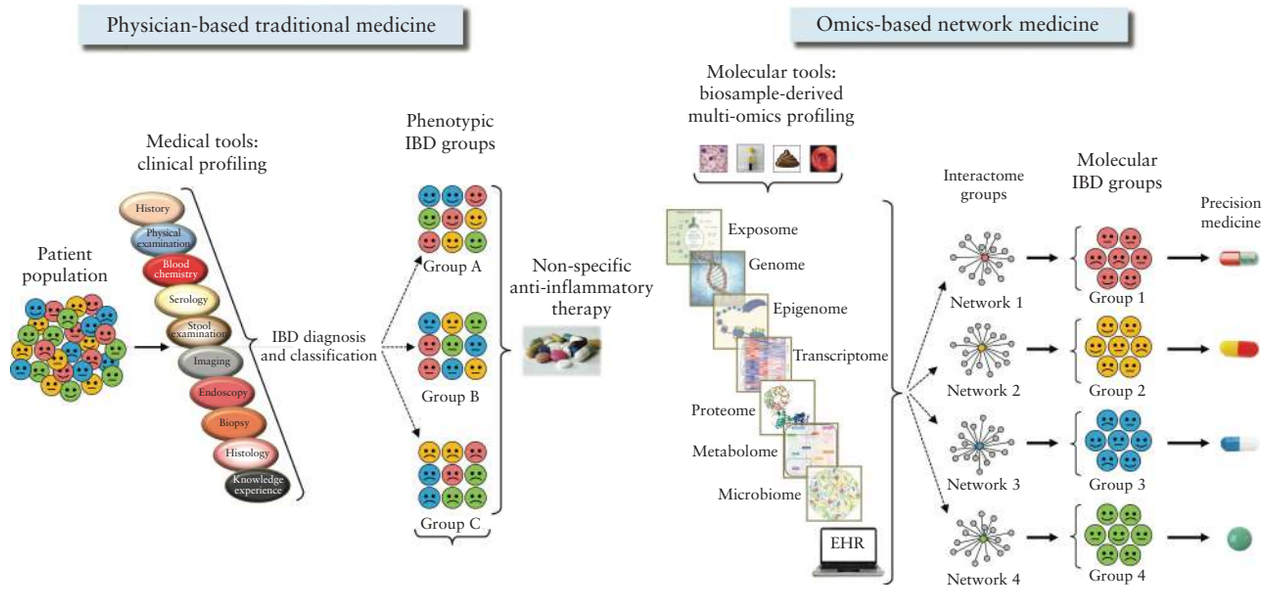
DrugMatrix includes results from gene-expression experiments from different rat tissues at different time points and drug doses.[252] The Open Toxicogenomics Project-Genomics Assisted Toxicity Evaluation Systems [TG-GATEs] stores gene-expression profiles and toxicological data [biochemistry, haematology, histopathological images] from in vivo [rats] and in vitro [rat and human] assays on 170 compounds, including known hepatotoxic and nephrotoxic drugs.[253] ConsensusPathDB is a meta-database for molecular interactions and pathways which integrates 32 public resources, consists of more than 600 000 unique interactions of different types, and holds more than 5000 human pathway concepts.[254,255] ToxDB integrates toxicogenomics data from Open TG-GATEs and DrugMatrix, with pathway concepts from ConsensusPathDB, and contains treatment datasets covering 437 drugs.[256] With these tools, researchers can search for associations of drugs with specific molecular pathways and discover which mechanisms of action lead to toxicity. Computational tools have also been developed to query the databases for similarities in gene signatures as in the CMap.[257] Additional computational models have recently been developed using machine-learning algorithms to predict drug liver toxicity.[258]

3.5.3. Network validation in IBD cellular and animal models

As discussed above, several computational tools exist for the construction of IBD networks, identification of new pathways and therapeutic targets, and for discovery of new drugs theoretically effective for IBD PM. As correct and precise the results from these in-silico systems might be, subsequent validation in cellular or animal model systems is still required, at least for the foreseeable future.

3.5.3.1. IBD networks

By integrating the IBD gene regulatory network described by Jostins *et al.*[107] with gene expression data from intestinal samples from three independent patient cohorts, Peters *et al.*[259] built a predictive network model. In this model, the authors found a conserved inflammatory component [CIC], identified driver genes predicted to modulate the regulatory states of the IBD network, and experimentally validated the driver genes in human macrophages and IBD animal models. As IBD knowledge expands, the IBD CIC network could provide a framework to enable a more complete understanding of regulatory components of IBD and the discovery of novel therapeutic targets.



Comparison of traditional medicine and network-driven IBD therapy

Figure 4. A graphic representation of the way that IBD therapy is provided by physician-based traditional medicine compared with how omics-based network medicine can provide precision medicine. In the first scenario, subjects from the general patient population [different colours with different facial expressions] seeking medical advice because of suspected IBD are submitted to a series of routine tests that usually include history, physical examination, blood work, serology, stool examination, imaging studies, ileocolonoscopy, and histopathological examination of mucosal biopsy samples. The combined results are then evaluated by the attending physician who, based on his or her level of knowledge and experience, makes a definitive or tentative diagnosis of IBD and classifies the patients into groups that are phenotypically similar [all smiling, serious, or sad] but not biologically homogeneous [mixed colours in each group]. Then, the patients are given some form of non-specific anti-inflammatory agent. In the second scenario [right panel], the same patients with suspected IBD provide biosamples [blood, serum, stools, biopsy sample] that are submitted to comprehensive omic analyses. The results are combined with data from electronic health records [EHR]. The integrated results reveal the biological network of each patient or group of patients [ie, the individual IBD interactomes] and allow for the classification of patients in biologically homogeneous [same colour in each group] at the molecular level but not necessarily phenotypically similar [mixture of smiling, serious, or sad]. Then, based on the underlying biological network, each patient or group of patients are given a medication that specifically targets the hub[s] of the disease module[s] in the IBD interactome and, in so doing, implements PM for the patients. IBD, inflammatory bowel disease.

A systems pharmacology model for IBD has recently been proposed based on the main cells and proteins involved in the pathobiology of the disease, thus building a 'post-transcriptional' network.[260] This model represents an additional tool for the identification of new IBD biomarkers, integration of IBD polymorphisms to identify responders and non-responders, and discovery of potential therapeutic targets.

3.5.3.2. Drug discovery

The application of drug repositioning for IBD has already been considered.[261] Such an approach was first reported in 2011, when CD gene signatures were queried in CMap based on the hypothesis that a compound with the opposite molecular signature could become a new therapeutic agent. Prednisolone and the anticonvulsant topiramate were found to have good therapeutic potential, and topiramate was shown to reduce inflammation in a colitis rat model.[262] Since then, several drug-repositioning studies have been published using the CMap, LINCS, or similar computational programs. Using DrugBank, drugs that target the proteins encoded by IBD candidate genes were identified and included known IBD drugs, drugs currently investigated in IBD, drugs used or currently investigated for other inflammatory conditions, and investigational drugs not yet registered for clinical use.[263] Although these reports demonstrate the potential of drug repositioning for new IBD drug discovery, the findings must be validated in in vitro and in vivo models before being considered as serious candidates for IBD therapy.

3.5.3.3. Drug toxicity and drug response

Genetic markers for thiopurine toxicity have long been known. Thiopurine methyltransferase [*TPMT*] gene variants [which have been widely studied and incorporated into clinical practice to guide thiopurine use and dosing][264] and the recently discovered nudix hydrolase 15 [*NUDT15*] variants are associated with myelosuppression.[129,265] *HLA-DQA1-HLA-DRB1* variants are linked to the risk of developing pancreatitis.[266] Regarding biologic drugs, *HLA-DQA1*05* is associated with development of antibodies to both infliximab and adalimumab.[267] To better understand the pathways and mechanisms involved in drug effects, these findings on genetic markers of drug toxicity must be incorporated in IBD networks, and this may help assess the effect of a given drug in a given patient administered PM-based therapies.

4. Key Messages

- IBD is a biologically complex disease with a multifactorial aetiopathogenesis, characterised by patient heterogeneity and clinical, temporal, and therapeutic variability.
- Current therapeutic approaches do not capture the complexity, heterogeneity, and variability of IBD, and consequently fail to provide specific and durable beneficial effects.
- PM is a new concept that considers the biological complexity of IBD and the heterogeneity and variability of individual patients.

- Network medicine is an approach that embraces all the components [omes] of IBD and, by using computational tools, integrates them into a network called the IBD interactome.
- By analysing the IBD interactome, the key molecular drivers of gut inflammation can be identified and targeted by specific drugs with a greater chance of therapeutic success.
- The identification of IBD patient subtypes through computational approaches is key to developing PM therapeutics for IBD which have greater efficacy and fewer side effects.

5. Summary and Outlook

Recent decades have witnessed major advances in the understanding of IBD at the bench and its management at the bedside. These advances have been translated into a new armamentarium of therapeutic agents that target individual components of gut inflammation, such as cytokines, receptors, adhesion molecules, and signalling pathways. A therapeutic effect is observed, but this benefits only a portion of IBD patients to a variable and unpredictable degree, and the effect is frequently lost over time. This disappointing situation makes it clear that, despite the recent progress achieved in the management of IBD, we are still far from optimal results. Two of the main reasons for this failure are that current IBD drugs are non-specific anti-inflammatory agents or biologics that block single targets of a complex multifactorial biological process. Thus, the next step is to develop agents that specifically target the key controllers of IBD biological complexity. This requires the adoption of advanced bioinformatics tools, such as systems biology, that integrate all components of the disease process into a network medicine approach that allows the implementation of PM in IBD [Figure 4]. Therefore, in a decade or so, IBD therapy will undergo an inevitable major shift from the traditional physician-based approach, that uses broad anti-inflammatory agents to treat phenotypically similar but biologically heterogeneous IBD patients, to an omics-based network medicine approach that treats molecularly homogeneous IBD patients with highly specific and customised PM drugs.

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Author Contributions

All authors contributed equally to the concept and design of the study, to the acquisition, analysis, and interpretation of data, and to the drafting and critical revision of the article for intellectual content. All authors approved the version being submitted.

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