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Review

Dynamic profiling in inflammatory Bowel disease: A manifesto for personalized care

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ABSTRACT

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, is a heterogeneous chronic condition whose clinical management has been advanced by the availability of molecularly targeted therapies. Despite this progress, marked inter- and intra-patient variability limits the effectiveness of a one-size-fits-all treatment approach. Precision medicine is a promising solution, but its implementation in routine care is limited. In this manifesto, we propose a multidimensional conceptual framework for the dynamic clinical profiling of IBD patients to be used in real-world clinical settings. Here, we first review key aspects of gut mucosal immunology, including epithelial–immune–stromal interactions and "angry" immune cells as mechanistic drivers of therapeutic variability. We then discuss five domains that are critical for clinical decision making in IBD: disease complexity (phenotype, history, and prior therapeutic exposure); patient frailty and comorbidities; extraintestinal manifestations; patients' needs and preferences; and sustainability. Integrating these domains into

Abbreviations: APC, antigen-presenting cell; CD, Crohn's disease; EIM, extraintestinal manifestation; IBD, inflammatory bowel disease; IEC, intestinal epithelial cell; IL, interleukin; IPAA, ileal pouch-anal anastomosis; JAK, Janus kinase; MSC, mesenchymal stem cell; POR, postoperative recurrence; RCT, randomized controlled trial; S1P, sphingosine-1-phosphate; SDM, shared decision making; Th, T helper; TNF, tumor necrosis factor; Treg, regulatory T; UC, ulcerative colitis; VTE, venous thromboembolism.

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a treat-to-target strategy requires the iterative reassessment of patients and the acknowledgment of the evolving nature of both the disease and the patient. We then provide general recommendations for incorporating these elements into the choice of therapy. Finally, we argue that future IBD care should merge the analysis of composite molecular signatures with holistic, patient-centered, dynamic clinical profiling to guide treatment choice, monitoring, and de-escalation. By reframing personalized medical care as a continuous process – a dynamic profiling – rather than a static assessment, this framework should optimize therapeutic outcomes, enhance patients' quality of life, and improve the sustainability of IBD care.

1. Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, relapsing condition that presents with a wide range of symptoms. Molecularly targeted therapies (from now on referred to as 'advanced therapies' in this manuscript) are the cornerstone for treating moderate-to-severe IBD. These medicines include both therapeutic antibodies (here, called "biologics"), such as anti-tumor necrosis factor (TNF) antibodies (infliximab, adalimumab and golimumab), anti-integrins (vedolizumab), anti-interleukin (IL)-23 (ustekinumab [anti-IL23p40], and risankizumab, mirikizumab and guselkumab [anti-IL23p19]), and small molecule drugs, such as Janus kinase (JAK) inhibitors (tofacitinib, filgotinib and upadacitinib) and sphingosine-1-phosphate (S1P) receptor modulators (ozanimod and etrasimod). However, the optimal use of these drugs and their position in therapeutic pathways remain unclear: Comparative efficacy data are limited, and the one-size-fits-all approach is increasingly recognized as insufficient due to inter- and intra-patient variability. Such a variability is shaped by genetic, immunological and microbiological determinants, as well as by environmental exposures [1] – including diet, nutrition,

Fig. 1. Five domains for clinical decision making in IBD. CD, Crohn's disease; SGM, sexual and gender minorities; UC, ulcerative colitis; ADT, advanced therapies; CVE, cardiovascular events; VTE, venous thromboembolism.

pollution, and lifestyle, which contribute to the evolving and heterogeneous clinical profile of IBD and make patient profiling particularly challenging.

Precision (or personalized) medicine in IBD can be conceptualized through two lenses. In terms of basic and translational research, the molecular heterogeneity of IBD has been uncovered, but the integration of these findings into clinical practice remains limited. From a clinical standpoint, personalization of medical therapy is achieved when a treatment path is tailored to a patient's characteristics. Importantly, patients' needs and disease behavior change over time, so their clinical profiling must evolve from a static assessment to a dynamic process. This change requires reassessment and treatment adaptation based on the clinical course, treatment response, emerging comorbidities, and the patient's preferences and life circumstances.

This manifesto explores the evolving landscape of dynamic clinical profiling of IBD patients. We begin by reviewing recent insights from gut mucosal immunology that are relevant to personalized medicine. We then discuss five key domains of clinical decision making in IBD (Fig. 1): disease complexity, patient frailty and comorbidities, extraintestinal manifestations, patients' needs and preferences, and sustainability. Finally, although a comprehensive analysis of all the elements of clinical profiling in IBD is beyond the scope of this article, we end by providing a conceptual framework supported by examples.

2. Methods

This article was developed through a structured, multidisciplinary initiative aimed at identifying the key domains that should guide patient clinical profiling and personalized therapeutic decision making in IBD. A multidisciplinary group of clinicians and researchers with recognized expertise in IBD was convened, including gastroenterologists, a pharmacologist, a pharmacoeconomist, and a methodologist.

An initial in-person meeting was held to identify the main domains of interest, followed by a broad narrative literature review to explore conceptual frameworks and evidence relevant to those domains. The search, conducted in PubMed and EMBASE, included the following terms: *inflammatory bowel disease*, *Crohn's disease*, *ulcerative colitis*, *personalized therapy*, *disability*, *severity*, *complexity*, *perianal disease*, *postoperative recurrence*, *postoperative prophylaxis*, *frailty*, *comorbidities*, *safety*, *extraintestinal manifestations*, *cost*, *pharmacoeconomics*, *environment*, *shared decision-making*, and *patient preference*. Relevant articles were screened, and key concepts were extracted and synthesized.

Subsequently, the group met virtually to refine the emerging structure, discuss which domains were most relevant to patient profiling and clinical decision making in IBD, and examine the practical implications of each domain in clinical practice. The manuscript was reviewed and revised collaboratively by all authors. The final framework reflects a synthesis of available evidence and collective expert interpretation.

3. Gut mucosal immunology

IBD emerges from a complex interplay, called the “IBD interactome”, among the genome, immunome, microbiome and exposome [1]. Each of these domains has multiple components: the genome includes genes, non-coding DNA, and epigenetic traits [2–4]; the immunome includes innate and adaptive immune cells as well as non-immune cells like intestinal epithelial cells and fibroblasts that have immune functions; the microbiome consists of bacteria, viruses, archaea, and fungi; and the exposome encompasses lifetime environmental exposures. From a molecular perspective, IBD is not a uniform entity because patient-specific molecular signatures determine both disease phenotype and therapeutic response. Therapeutic failure may stem from genetic diversity, activation of diverse immune pathways over time [5,6], microbiota composition, or environmental influences. Indeed, environmental factors such as diet, smoking, air pollution, stress, and sleep disruption can modulate gut barrier integrity, immune cell function, and microbiome composition, thereby influencing both disease phenotype and treatment response over time [7,8]. The future challenge is to reframe this intricate web through the lens of precision medicine. In this section, we discuss immune mechanisms that cause inter- and intra-patient variability in IBD treatment response (Fig. 2).

A combination of IBD risk factors (both genetic and environmental) can alter epithelial barrier integrity, which allows luminal antigens to enter the gut wall. This event, in genetically predisposed individuals, is followed by an abnormal, exaggerated cytokine response that leads to chronic mucosal inflammation. In this context, intestinal epithelial cells (IECs, including Paneth cells, goblet cells and enterocytes), once viewed primarily as forming a barrier, are now recognized as immunologically active components that complement the role of innate immune cells [9]. IECs detect microbial signals (pathogen-associated molecular patterns and danger-associated molecular patterns) [10], and they secrete cytokines (IL-1β, IL-18, IL-25, IL-33) that shape immune responses [9]. Paneth cells release antimicrobial peptides such as α-defensins and lysozyme [11]. Goblet cells produce the antimicrobial proteins TFF3 and RELMβ [12], sample luminal antigens and present them to dendritic cells [13,14]. IECs, when in inflammatory conditions, express major histocompatibility complex molecules and interact with T cells [15]. In IBD, these processes are dysregulated: the production of antimicrobial proteins and the secretion of mucus falter, and overactivation of the inflammasome (a supramolecular complex that can orchestrate inflammatory responses within the cell) drives further damage [16]. Importantly, epithelial dysfunction may precede and drive overt inflammation, as suggested by the observation that certain polymorphisms related to epithelial function and integrity – such as in the *MUC2* (mucin 2), *NOD2* (Nucleotide-binding oligomerization domain-containing protein 2), and *XBP1* (X-box binding protein 1) genes – are associated with IBD susceptibility [17].

In the early phase of IBD, there is marked activation of innate immunity, the body's first line of defense, and this includes the activation of antigen-presenting cells (APCs). APCs, activated by pathogen- and danger-associated molecular patterns, present antigens to naïve T lymphocytes. During antigen presentation, the local cytokine environment drives the clonal expansion of T cells toward several immunological paradigms (Fig. 2): Th1, Th2, Th9, Th17, Th22 and Treg. In particular, T helper (Th) 1 cells produce TNF and interferon gamma (IFN-γ) and are associated with CD. Th2 cells, associated with UC, secrete IL-4, IL-5, and IL-13 [18]. One study found increased Th9 cells in UC: these cells produce IL-9 [19], which weakens barrier integrity and enhances Th17 cell activation. Th17 cells, whose levels are high in both CD and UC, mainly release proteins of the IL-17 family, which mediate intestinal damage; interestingly, IL-17 blockade does not reduce intestinal inflammation and can sometimes exacerbate it[20], possibly due to a role of these cytokines in barrier maintenance [20,21]. Th22 cells are upregulated in IBD, but their role is elusive. These cells secrete IL-22, which promotes wound healing [22] but can also fuel neutrophil-mediated inflammation when unopposed [23]. IL-22 binding protein, whose levels are also high in IBD, blocks IL-22 signaling and potentially impairs mucosal healing [24]. Finally, regulatory T cells (Treg) are increased but functionally defective in IBD patients [18], while $CD8^+$ T cells, upon chronic activation, can damage the intestinal epithelium [25].

T cell lineages are not terminally fixed but rather exhibit remarkable plasticity, under the influence of the cytokine milieu and microbial signals [26]. Under pro-inflammatory conditions, Th17 cells can also assume Th1-like features and produce both IL-17 and IFN-γ, thereby developing high pathogenic potential [27]. Tregs, during chronic inflammation, can downregulate their expression of FoxP3, which reduces their regulatory capacity, and they can acquire pro-inflammatory properties, including the production of IL-17 or IFN-γ [28].

Chronic antigen stimulation can lead to T cell exhaustion, which is a dysfunctional state characterized by reduced functions and high expression of inhibitory receptors [29]. Notably, exhausted T cells can be either completely dysfunctional (terminal exhaustion) or retain

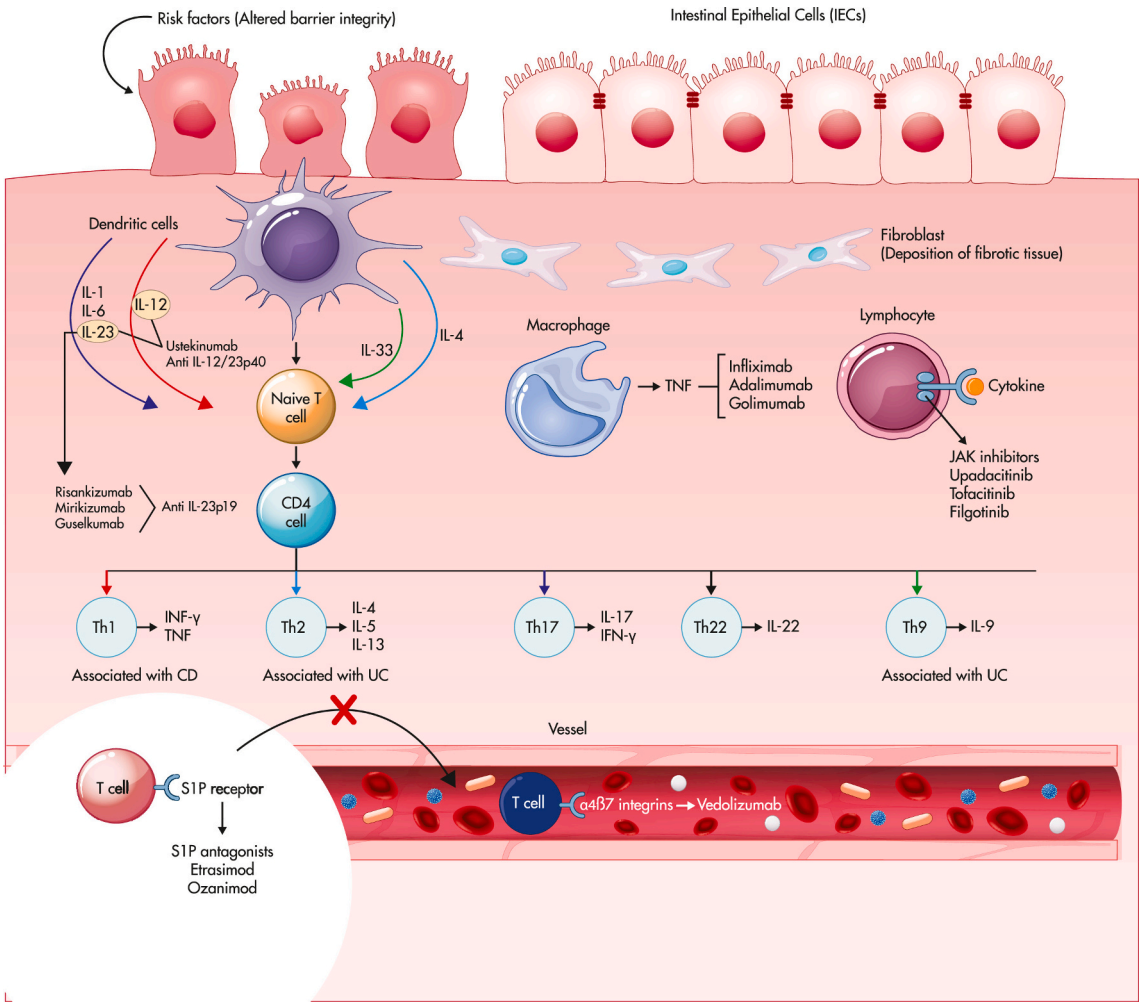

Fig. 2. The gut mucosal barrier: key pathogenic mechanisms in IBD, therapeutic targets and corresponding medicines. CD, Crohn's disease; IL, interleukin; INF, interferon; JAK, Janus kinase; Th, T helper; TNF, tumor necrosis factor; S1P, sphingosine-1-phosphate; UC, ulcerative colitis.

partial activity (progenitor exhaustion) [30]. Exhausted Th cells and $CD8^+$ T cells can mitigate intestinal inflammation by reducing their inflammatory functions [31–33]. A recently identified subpopulation of exhausted IL-26^+ $CD8^+$ T cells acquires innate-like characteristics and seems to exert regulatory functions [34]. However, exhausted Th cells and $CD8^+$ T cells may also have a pathogenic role via impaired microbial clearance and wound healing. Incomplete exhaustion, in particular, is thought to fuel persistent low-grade inflammation [35–37]. It is worth noting that Treg cell exhaustion has a clear pathogenic role that compromises immune regulation [38].

Macrophages play a central role in the pathogenesis of IBD, by contributing to both inflammation and tissue remodeling. They are a heterogeneous, highly dynamic population of cells whose functions go beyond the basic M1/M2 classification (which describes two functional stages of macrophages, the first pro-inflammatory and the second anti-inflammatory), which fails to fully depict their complexity [39]. In active IBD, pro-inflammatory macrophages activate Th1 and Th17 cells, type 3 innate lymphoid cells, fibroblasts, and IECs [40]. Yet during IBD remission, the levels of $CD14^{high}$ macrophages (highly pro-inflammatory) decrease, while $CD206^+$ macrophages with anti-inflammatory functions reappear [41].

"Angry cells" – mostly T cells and macrophages – have emerged as a concept in IBD, where they purportedly sustain inflammation through autocrine loops, metabolic reprogramming, and resistance to inhibitory signals. Th cells expressing the IL-23 receptor have been associated with resistance to anti-TNF antibodies [40]. Defective IL-10 receptor signaling, seen in monogenic IBD (which are forms of IBD caused by a single gene variant) [41], can contribute to determine the macrophage "angry" state. Spatial transcriptomics has identified macrophage clusters (mostly including C-X-C motif chemokine 5 [CXCL5]-positive cells) that persist with strong TNF and IL-1 production despite biological therapy [42,43].

Increasing attention has been directed to the role of stromal cells in IBD pathophysiology. These cells have emerged as active players in shaping immune responses, sustaining chronic inflammation, and contributing to fibrosis and tissue remodeling. Stromal cells, particularly intestinal fibroblasts and myofibroblasts, interact with immune and epithelial cells through their production of cytokines and extracellular matrix components, and thus affect both disease progression and therapeutic outcomes. In particular, fibroblasts have significant plasticity and, under inflammatory stimulation, can differentiate into myofibroblasts that resist apoptosis and synthesize large amounts of protein, leading to pathological deposition of fibrotic tissue and subsequent stricture formation [44,45]. Alternatively activated macrophages contribute to fibrogenesis by promoting myofibroblast differentiation and extracellular matrix deposition. In turn, myofibroblasts recruit and activate pro-fibrotic macrophages, forming a self-sustaining loop [46–48].

Given this complexity, it is perhaps not surprising that research has fallen short in identifying immune biomarkers to predict therapy response. IBD, more than a diagnosis to treat, needs to be interpreted as a dynamic state to reiteratively decode. Perhaps the most transformative

aspect of research will be the effort to integrate these domains (immune, genetic, microbial, and environmental) into a comprehensive stratification framework: rather than isolated biomarkers, future precision medicine in IBD will need to rely on composite molecular signatures that should be periodically re-assessed.

4. Disease complexity

Conventional tools for IBD assessment focus on clinical, endoscopic, radiological, and histological activity. However, activity per se captures a mere snapshot of the disease, often overlooking the actual burden of IBD, characterized by cumulative damage and increasing disability [49]. Moderate-to-severe clinical activity and steroid dependence or refractoriness are the standard criteria for initiating advanced therapies [50,51]. Yet, more nuanced evaluations often guide the decisions of when to initiate treatment and which therapy to choose; these evaluations consider symptoms, inflammatory burden, and additional factors that reflect the risks of disease progression, complications and reduced quality of life. Peyrin-Biroulet et al. proposed, in 2016, a model of IBD severity with three core domains: impact of the disease on the patient, disease burden and disease course [52]. This model has led to the development of disease severity indexes for the quantitative assessment of severity. This section explores factors that contribute to IBD complexity and burden, beyond the sole disease activity, and focuses on disease history and phenotype (Fig. 3). Other aspects of disease severity (frailty, extraintestinal manifestations, impact on patients) are discussed in later sections.

Prior exposure to advanced therapies is a key factor that influences IBD outcomes, with biological drug-naïve patients generally experiencing more favorable outcomes when treated with advanced therapies compared to exposed ones. Most comparative efficacy studies have compared such naïve patients to those already exposed to anti-TNF agents, while data from patients previously treated with other advanced therapies remain scarce. Network meta-analyses have found that anti-TNF agents (particularly infliximab) are among the most effective treatments for naïve patients; conversely, anti-IL-23p19 and

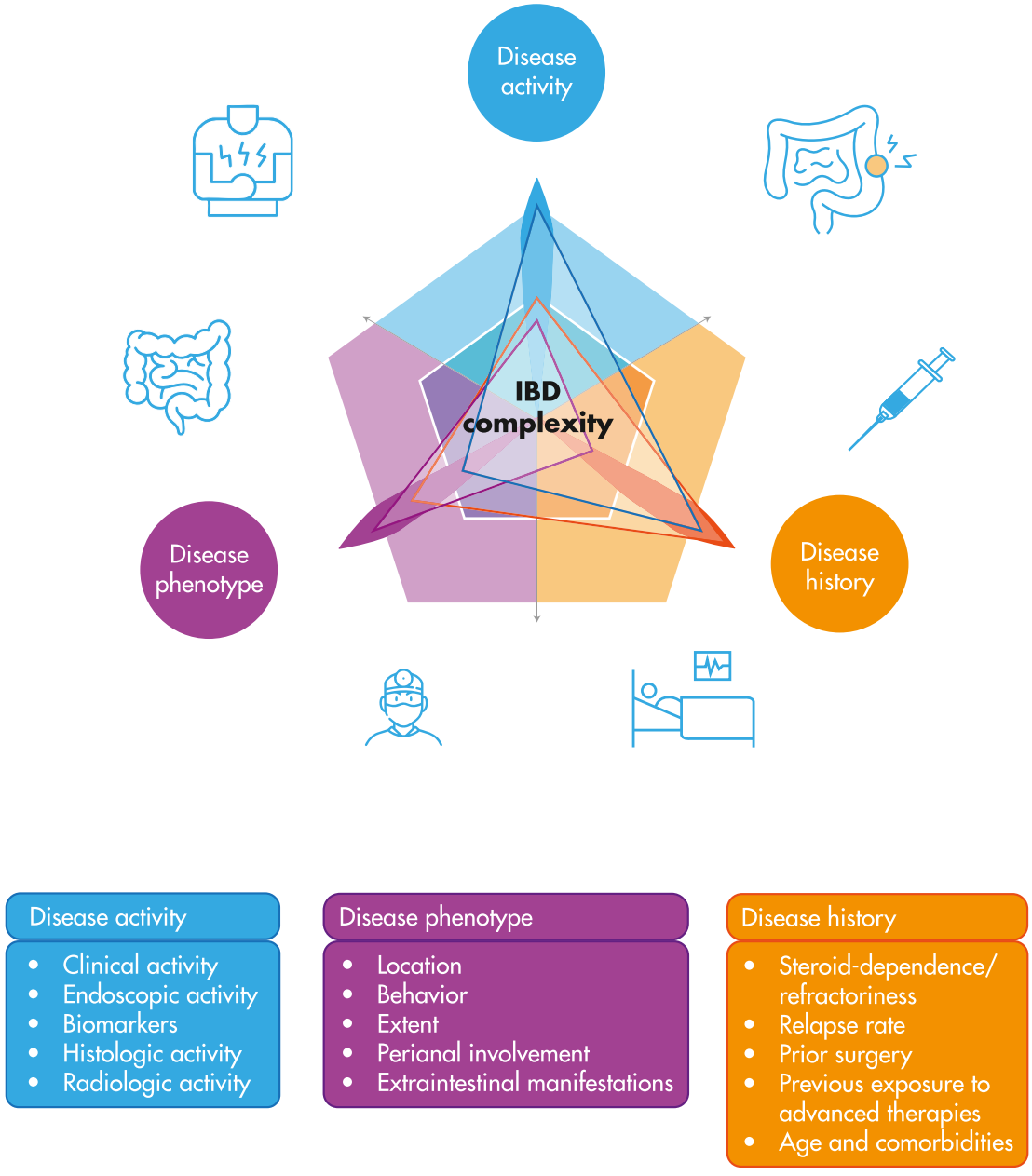

Fig. 3. IBD complexity and its determinants.

upadacitinib are ranked highest for the treatment of both naïve and exposed patients [53–57]. Infliximab, when combined with azathioprine, was found to lead to better outcomes than infliximab monotherapy in naïve patients with CD [58] and UC [59]. The VARSITY trial showed that vedolizumab is superior to adalimumab in naïve patients with UC [60]. Conversely, in the retrospective EVOLVE Study, vedolizumab and anti-TNF agents had comparable clinical effectiveness in naïve patients with CD or UC [61]. The SEAVUE trial found comparable outcomes for adalimumab and ustekinumab in naïve patients with CD [62]. However, some real-world data support a superiority of anti-TNF agents over ustekinumab in this population [63,64]. Real-world data strongly suggest that vedolizumab efficacy is reduced in patients previously exposed to anti-TNF antibodies [65–67]. In randomized controlled trials (RCTs), S1P receptor modulators exhibited significantly higher efficacy in naïve UC patients than in UC patients already exposed to anti-TNF antibodies [68,69]. In exposed patients with CD, real-world evidence suggests that ustekinumab is superior to vedolizumab [70], even though a retrospective study found similar efficacy for objective outcomes [71]. A recent network meta-analysis found that anti-IL-23p19 agents are superior to ustekinumab in CD patients previously exposed to anti-TNF agents [72]. This analysis included findings from the SEQUENCE trial, where risankizumab demonstrated superiority to ustekinumab [73]; nonetheless, the open-label design and the use of a non-inferiority-to-superiority hierarchical testing strategy warrant cautious interpretation of these findings. In the VIVID trial, mirikizumab was non-inferior to ustekinumab for clinical outcomes but did not achieve superiority for endoscopic endpoints, despite numerically higher rates of both clinical and endoscopic response among biologic-exposed patients [74]. The GALAXI program, on the other hand, demonstrated the superiority of guselkumab over ustekinumab for both endoscopic and composite (clinical and endoscopic) outcomes, including deep remission (defined as the combination of clinical and endoscopic remission), in a population of biologic-naïve and biologic-exposed patients [75]. Notably, guselkumab showed a more consistent advantage across both outcomes in exposed patients, whereas in naïve individuals the benefit was limited to endoscopic endpoints. However, it is important to note that neither the VIVID nor the GALAXI trials were specifically powered to establish superiority over ustekinumab. For UC patients exposed to anti-TNF agents, JAK inhibitors and ustekinumab were found to be superior to vedolizumab in three multicenter studies [76–78] but not in a fourth such study [79]. Data on the comparison between JAK inhibitors and anti-IL-23 agents are scarce, but recent findings suggest a superiority of tofacitinib over ustekinumab as third-line therapy in UC [80].

Disease phenotype, namely disease location and extent, is also a critical issue. In CD, ileal involvement >40 cm and upper gastrointestinal localization are associated with worse outcomes [81,82]. Conversely, isolated colonic CD was found to have a lower risk of intestinal complications and a trend toward a higher response to drugs [83]. Extensive UC is associated with increased risks for relapse, hospitalization and colorectal cancer [84–86]. Isolated proctitis is understudied, as it is usually excluded from RCTs. Anti-TNF antibodies, vedolizumab, and JAK inhibitors were effective in observational reports (reviewed in [87]). Interestingly, a recent retrospective study showed that biological drug-naive status and vedolizumab positively correlated with better outcomes in patients with ulcerative proctitis [88]. Etrasimod is the only drug that has been evaluated for isolated proctitis in an RCT, where it showed superiority over placebo at week 12 [89]. Notably, proctitis can extend proximally, which correlates with poorer outcomes [90]. Strategies to prevent proximal extension should be explored.

CD complications, including strictures and enteric fistulas, require individualized management. For strictures, surgery is often necessary, but some patients benefit from medical therapy. In the prospective CREOLE study, 50.7% of patients with symptomatic strictures treated with adalimumab remained surgery free four years after treatment initiation [91]. The retrospective USTEKNOSIS study suggested that ustekinumab is beneficial for anti-TNF-exposed patients with strictures [92]. Finally, real-world observations also suggest that vedolizumab may be effective in these patients, either as monotherapy [93] or in combination with other advanced therapies [94]. For non-perianal penetrating disease, observational studies reported effectiveness of anti-TNF antibodies [95–99], but medical treatment must be carefully weighed against surgery for these patients.

Incorporating the assessment of disease complexity into clinical decision making is challenging. As patients with more complex IBD face higher risks of surgery, hospitalization, and disability, the risk-benefit ratio should favor more effective treatments, even if these are riskier or costlier. Furthermore, IBD complexity should also guide the frequency of patient monitoring and the decision to de-escalate therapy in stable patients. Importantly, the concept of a therapeutic window of opportunity has gained traction, especially in CD. Emerging evidence suggests that early, intensive treatment initiation can modify the disease course and reduce long-term complications and the need for surgery [100]. The recent PROFILE trial showed that a top-down approach improved clinical and endoscopic outcomes compared with conventional step-up management in patients with newly diagnosed CD, regardless of biomarker-based baseline risk stratification [101]. Similarly, the LOVE-CD trial demonstrated superior outcomes in patients with early vs. late CD treated with vedolizumab [102]. These findings support the integration of early treatment with advanced therapies into the clinical profiling of CD patients, to potentially reduce long-term complications and disability.

How clinical decisions in CD can be guided by risk stratification based on disease complexity, rather than on luminal disease activity, is here illustrated in two scenarios: therapy for complex perianal CD and prophylaxis of postoperative recurrence.

4.1. Complex perianal CD

Perianal CD affects approximately 20% of CD patients [103] and presents with anal canal lesions, anal strictures, fistulas and abscesses. Complex perianal CD is characterized by a combination of high anal fistulas, often with multiple external fistulous openings, rectovaginal fistulas, abscesses, anorectal strictures, and rectal inflammation [104]. The outcome of complex perianal CD is worse than that of non-perianal CD, because of the higher risks of hospitalization, IBD-related surgery, and anorectal cancer [105] and the higher probabilities of progressing to stricturing or penetrating disease [106]. Collectively, these data constitute the rationale for a top-down approach – starting with the most effective treatments early in the disease course – to complex perianal CD, to prevent long-term complications and unfavorable outcomes.

Guidelines of the European Crohn's and Colitis Organisation recommend surgical drainage before medical or surgical therapy for complex perianal CD and, for amenable patients, a combination of medical and surgical therapy [107]. Two RCTs found that infliximab was efficacious in inducing a fistula response and fistula remission [108,109]. Adalimumab was found to be superior to placebo in inducing fistula remission in a subgroup analysis of the CHARM trial [110], and these findings were subsequently confirmed in an RCT [111]. A 2023 network meta-analysis corroborated these findings, showing that anti-TNF agents are superior to placebo and infliximab is superior to adalimumab in inducing a fistula response [112]. The sensitivity analysis of a 2024 network meta-analysis, which included only studies with fistula-related primary outcomes, confirmed the superiority of anti-TNF agents over placebo for both the induction and maintenance of remission; furthermore, the combination of an anti-TNF antibody and an antibiotic was superior to anti-TNF monotherapy [113]. Notably, four studies observed that higher trough levels of infliximab or adalimumab associate with better outcomes in patients with perianal CD [114–117].

Evidence for the efficacy of non-anti-TNF agents is less robust. Post-hoc analyses of RCTs demonstrated higher rates of fistula remission for

both vedolizumab [118] and ustekinumab [119] than for placebo, although the differences did not reach statistical significance. In the abovementioned 2023 network meta-analysis, ustekinumab was found to be superior to placebo for inducing a fistula response but not fistula remission [112]. A subsequent meta-analysis found ustekinumab to be effective in maintaining a fistula response, whereas vedolizumab did not achieve statistical superiority over placebo for any fistula-related outcome [113]. In a post-hoc analysis of registration trials, upadacitinib showed superiority over placebo in inducing the resolution of fistula drainage and closure of external openings [120].

Mesenchymal stem cell (MSC) therapy has emerged as a promising treatment option for complex perianal CD. The pivotal ADMIRE-CD trial demonstrated that a local injection of allogeneic adipose-derived MSCs (darvadstrocel) significantly increased the combined remission rates (closure of external openings and absence of collections on magnetic resonance imaging) at 24 and 52 weeks compared to placebo [121]. However, a preliminary analysis of a subsequent trial (ADMIRE-CD II) did not confirm the significant difference in combined remission rates between darvadstrocel and placebo at 24 weeks [122]. Besides allogeneic MSCs, autologous MSCs are being tested in observational research. Several studies have reported a potential benefit of this therapy on perianal CD [123–125], but further studies are needed.

4.2. Postoperative CD recurrence

Despite therapeutic advances, up to 50% of patients with CD still undergo intestinal resection (most commonly ileocecal or ileocolonic resection [126]) within 10 years of diagnosis [127]. After resection, postoperative recurrence (POR) is common. Endoscopic lesions and clinical symptoms are observed in three-quarters and one-third of patients, respectively, at one year [128], and the surgical recurrence rate is about 25% at 5 years [129]. Here, we focus on monitoring and treatment strategies to prevent POR, which we believe can serve as a paradigmatic example of individualized, risk-based therapeutic decision making. Regarding the treatment of symptomatic relapse after surgery, most data derive from observational studies [130]. Still, in the absence of definite evidence, therapeutic indications can be extrapolated from RCTs, assimilating POR to moderate-to-severely active CD.

The seminal work by Rutgeerts et al. from 1990 demonstrated that early endoscopic POR is predictive of subsequent clinical progression [131], supporting the rationale for early intervention. The current standard of care is early postoperative endoscopy (at 6–12 months) [132] for all patients, in accordance with the POCER study which found that treatment escalation guided by early endoscopy reduced the rates of endoscopic – but not clinical – recurrence at 18 months [133]. Three main strategies for the management of POR have been proposed: 1) endoscopy-driven treatment, where pharmacological therapy is initiated in patients with early endoscopic POR; 2) systematic early prophylaxis, where therapy is started in all patients within 8 weeks of surgery; and 3) risk stratification, where prophylaxis is started in patients at high risk of POR (even though consensus is lacking on what constitutes a high-risk patient) [134]. Risk factors for POR have an additive effect [135] and include current smoking, multiple prior resections, penetrating disease behavior, and perianal disease [136]. Less consistent evidence has also been presented for male sex, younger age at diagnosis, disease duration, and positive margins at resection [137]. In addition, growing evidence suggests that the type and configuration of the intestinal anastomosis may influence the rate of endoscopic POR [138]. In particular, a Kono-S anastomosis (a wide, antimesenteric, functional end-to-end handsewn anastomosis) has been associated with lower rates of endoscopic recurrence compared with conventional stapled anastomoses in observational studies [139], although other works did not support these findings [140] and confirmatory data from randomized trials are still awaited.

An RCT by Ferrante et al. did not find differences between systematic prophylaxis and endoscopic-driven treatment with thiopurines in preventing endoscopic POR [141]. Conversely, in two retrospective studies, prophylaxis was superior to endoscopic-driven management in preventing endoscopic, but not clinical, POR [142,143]. A 2021 study found that the risk of clinical recurrence 3 years after surgery, in patients with a Rutgeerts' score of at least i3 at early endoscopy, was less in those who received therapy after endoscopy than in those not treated [144]. In the same study, patients who received prophylactic therapy were more likely to maintain endoscopic remission and had a lower risk of clinical POR during follow-up. In the POCER study, patients with at least one risk factor for POR were treated with thiopurines and compared to those without such risk factors, who received a 3-month course of metronidazole; no differences were observed in the rate of endoscopic or severe endoscopic POR [133]. In a 2023 retrospective study, early prophylaxis was superior to an endoscopy-driven approach for preventing endoscopic POR only in patients with at least one risk factor [142], while Dragoni et al. observed that early prophylaxis was not superior to the endoscopy-driven approach in patients with only one risk factor [145]. One argument against early prophylaxis is the risk of overtreatment. However, in the PORCSE study, cumulative biological drug use was comparable between the proactive and reactive treatment groups, suggesting that a more conservative approach only delays the use of these drugs [143]. Notably, a retrospective study that assessed the impact of POR management strategies over 40 years found no significant reduction in surgical recurrence despite increasing use of immunosuppressants and biologics [146]. These results question the impact of these drugs on the disease's natural history and suggest that drug use is suboptimal in the postoperative setting.

Regarding specific treatments, anti-TNF agents are the most investigated drugs for POR prevention. Two RCTs demonstrated infliximab superiority over placebo in preventing endoscopic – but not clinical – POR [147,148], and another one observed reduced clinical POR [149]. No placebo-controlled RCT for adalimumab has been published, but a 2013 RCT demonstrated its superiority over azathioprine and mesalamine for prevention of both endoscopic and clinical POR [150]. A post-hoc analysis of the POCER study also supports the superiority of adalimumab over azathioprine in preventing endoscopic POR [151]. In contrast, a subsequent RCT did not confirm this superiority [152]. Finally, in a 2021 meta-analysis that pooled individual participant data from six studies, anti-TNF drugs proved superior to thiopurines in preventing clinical and endoscopic POR [153]. The REPREVIO study showed that early treatment with vedolizumab reduced endoscopic recurrence compared to placebo, but no difference in clinical POR was observed [154]. Observational data suggest that ustekinumab prophylaxis is also effective – and possibly superior to thiopurines – in preventing POR [155–157].

5. Patient frailty and comorbidities

5.1. Frailty

Frailty is garnering increasing attention in medicine and poses an additional challenge in the management of IBD patients (Fig. 4). Despite lacking a standardized definition, frailty is generally recognized as a multidimensional syndrome marked by diminished physiological reserve and impaired ability to cope with stressors, resulting in heightened vulnerability to adverse health outcomes [158]. Crucially, although influenced by chronological age and comorbidities, frailty is not entirely explained by either.

Several validated tools exist for frailty assessment, yet there is no consensus on the optimal screening method – particularly in the context of IBD. Commonly used tools for frailty assessment in IBD, such as the Fried Frailty Phenotype [159] and the FRAIL Questionnaire [160], are not disease specific [161]. Importantly, frailty and disability are distinct constructs: frailty reflects a state of diminished physiological reserve and vulnerability to stressors, whereas disability captures the functional impact of disease on daily life. Nonetheless, some IBD-specific

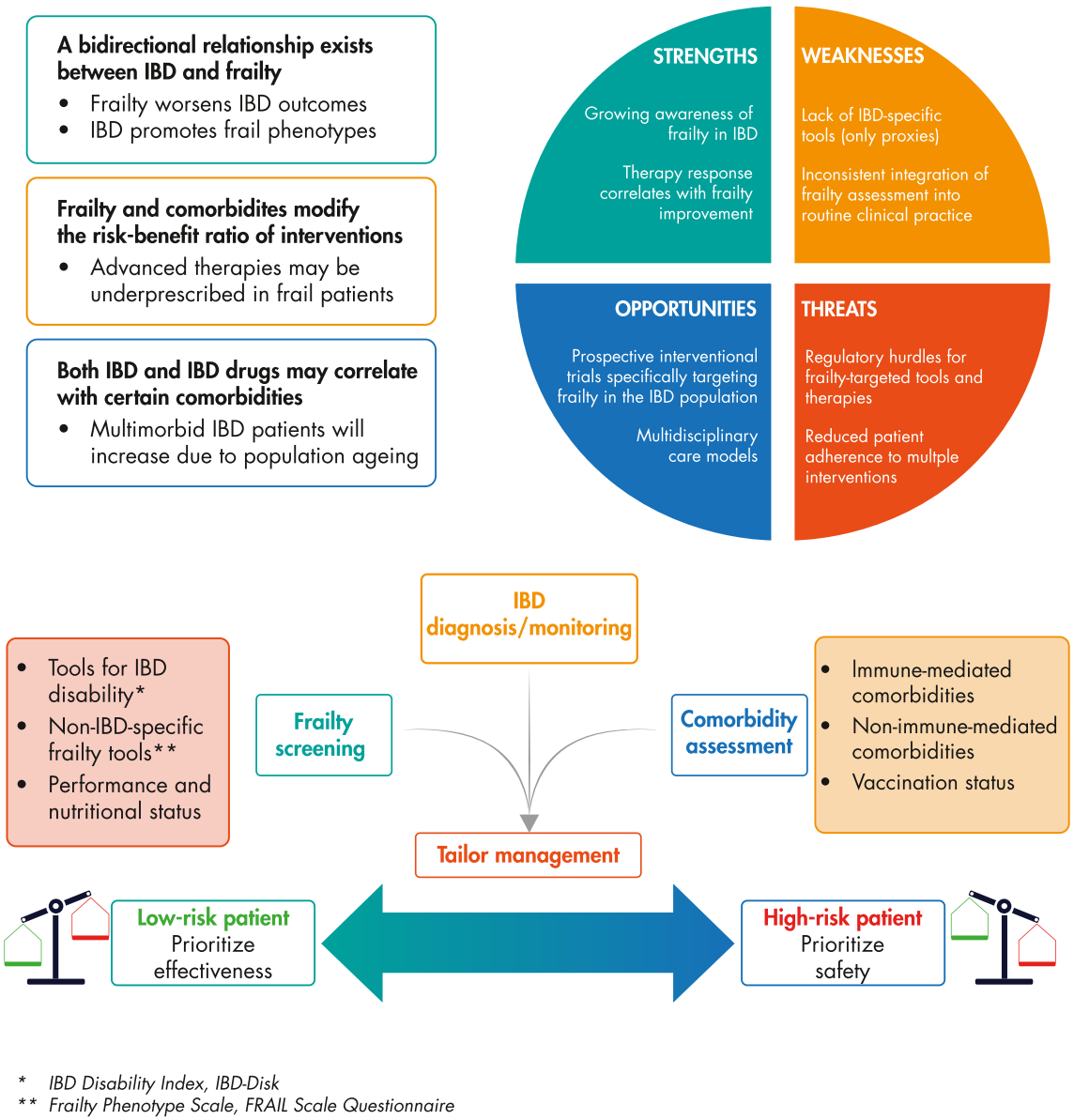

Fig. 4. Frailty in IBD.

instruments assess domains that partially overlap with and can serve as proxies for frailty. These tools include the IBD Disability Index, which is a validated, physician-administered tool [49], and the IBD Disk, which is a shorter, patient-administered adaptation of the former [162]. Several molecular markers of frailty have been proposed (reviewed in [163]). Because the serum levels of some of these biomarkers correlate with inflammation (e.g. IL-6, C-reactive protein) or disease activity (e.g. hemoglobin, albumin), there are concerns about their validity in the context of IBD. Future research should aim to develop IBD-specific frailty tools and identify frailty biomarkers independent of disease activity.

Frailty prevalence in IBD ranges from 6% to 54%, depending on the population investigated and the methodology used [164]. Frailty in IBD affects all age groups [165], but its prevalence increases with age and is higher in elderly IBD patients than in age-matched controls [166]. A bidirectional relationship links IBD and frailty: Frailty worsens IBD outcomes, including morbidity, mortality, healthcare use [166,167], quality of life and functional status [168]. Moreover, IBD itself promotes a frail phenotype, according to a Mendelian randomization study that found a positive causal link between IBD and frailty [169]. The risk of frailty in IBD patients is also associated with specific nutritional deficiencies and electrolyte imbalances, overall malnutrition and sarcopenia, all driven by chronic inflammation, malabsorption and, in more severe cases, intestinal insufficiency [170–172]. Uncontrolled gastrointestinal symptoms and subsequent psychological distress can exacerbate anxiety and mood disorders, which further compound the frailty burden [173–175]. Additionally, some IBD therapies increase the risk of infections, thromboembolic events, and certain malignancies [161,176].

A Norwegian population-based study revealed that frail older patients with IBD are less likely to receive biological therapy [177]. Indeed, frailty modifies the risk-benefit ratio associated with a certain intervention, so an individualized therapeutic approach is needed. In this regard, vedolizumab, ustekinumab and anti-IL-23p19 agents may have better safety profiles than other advanced therapies, particularly regarding infection and malignancy risk [176,178]. Of note, some evidence suggests ustekinumab is associated with a lower incidence of infections than vedolizumab, at least in certain IBD populations [179,180]. Control of intestinal inflammation is crucial in frail patients, as emerging data suggest that the response to biologics may improve frailty status in IBD [181,182]. In the general population, interventions

that reduce frailty have been found to improve overall health outcomes [183], including nutritional optimization, physical rehabilitation, management of sarcopenia through exercise and protein supplementation, and psychosocial support, but prospective interventional studies are needed to investigate this possibility in the IBD population. In clinical practice, nutritional assessment should prompt targeted interventions, such as dietary counseling and oral supplementation; resistance training and aerobic exercise programs represent a feasible, low-risk adjunct to medical therapy; systematic screening for anxiety and depression and referral to psychological support services complete the multidimensional approach to frailty mitigation. Frailty assessment may also guide decisions on procedures. For instance, surveillance colonoscopy may be unnecessary in patients over 75 years of age without prior dysplasia, considering the higher procedural risks [184] and limited benefit in this population [185].

5.2. Non-immune-mediated comorbidities

Non-immune-mediated comorbidities influence the management of IBD. While the presence of comorbidities is not necessary or sufficient to define frailty, they contribute to a frail phenotype and limit treatment choices. This issue is becoming increasingly relevant, as rising IBD incidence and population aging are increasing the number of elderly people with IBD, which is more likely to present with multimorbidity [186–188].

The risk of cancer in IBD patients has long been a concern due to the immunomodulatory actions of IBD drugs. Nevertheless, according to current evidence, advanced therapies do not significantly increase the overall risk of new or recurrent malignancy in the IBD population [189]. The risk of specific malignancies, however, may be higher. Some studies found that anti-TNF agents were associated with a slightly increased risk of melanoma, while a meta-analysis found that the evidence was inconclusive [190–192]. These drugs, particularly when administered in combination with thiopurines, were also associated with some types of lymphoma in some studies [193–195] but not in others [196,197]. The ORAL Surveillance study of patients with rheumatoid arthritis found that the incidence of certain malignancies in older patients with cardiovascular risk factors was higher when they were treated with tofacitinib than with anti-TNF drugs [198]. Whether this finding is generalizable to IBD patients is not yet known. So far, there is no evidence for an overall increased risk of cancer due to treatment with vedolizumab or anti-IL-23 agents [189]. Nonetheless, physicians treating IBD patients with a recent history of cancer need to take extra caution when prescribing therapy; although current evidence does not demonstrate an increased risk of malignancies associated with IBD therapies, the mechanisms of immunomodulators theoretically raise the possibility of promoting growth of subclinical tumors: therefore, caution is still warranted.

Cardiovascular and thromboembolic risks also deserve careful consideration, considering that chronic systemic inflammation per se is a recognized driver of atherosclerosis and endothelial dysfunction [199]. Active IBD is strongly associated with an increased risk of venous thromboembolism (VTE) [200], and prophylactic anticoagulation is recommended during severe disease flares in hospitalized IBD patients [201]. Additionally, three meta-analyses found an overall increased risk of cardiovascular disease in IBD patients [202–204], although the evidence is less consistent compared to that on VTE. JAK inhibitors have been associated with lipid profile alterations [205], so their use necessitates careful monitoring and eventual management. The ORAL Surveillance study revealed that, in older rheumatoid arthritis patients with cardiovascular risk factors, the rates of major adverse cardiovascular events and VTE were higher in patients treated with tofacitinib than in those treated with anti-TNF antibodies [198], but the generalizability to IBD patients is unknown. These findings prompted regulatory safety warnings and highlight the importance of cardiovascular screening prior to initiating a JAK inhibitor. Their use is not recommended by EMA in patients with at least one cardiovascular risk factor – especially those over 65 years – unless no suitable alternative is available [206]. The impact of anti-TNF antibodies on cardiovascular risk in IBD patients is controversial, with inconsistent findings from different cohorts [207,208]. Some evidence indicates an association between anti-TNF therapies and exacerbations of congestive heart failure. For example, the ATTACH trial, which investigated if infliximab was efficacious against moderate-to-severe heart failure, reported increased hospitalization and mortality risks associated with the higher dose tested [209]. Accordingly, product labels advise against the use of anti-TNF agents in patients with advanced heart disease (NYHA class III–IV) [210].

6. Immune-mediated extraintestinal manifestations

IBD primarily affects the gastrointestinal tract but is accompanied by comorbidities in up to 50% of patients [211]. These can be broadly divided into: 1) immune-mediated (the focus of this section) that share some pathogenic mechanisms with IBD [212], and 2) non-immune, associated with chronic inflammation or IBD therapies [213] (discussed earlier).

The most common immune-mediated comorbidities include extraintestinal manifestations (EIMs) that affect the joints (axial and peripheral spondylarthritis, as well as dactylitis, enthesitis, and tenosynovitis), the skin (psoriasis, psoriatic arthritis, erythema nodosum, pyoderma gangrenosum), the eyes (uveitis, scleritis/episcleritis) and the liver (primary sclerosing cholangitis) [212]. Their onset can either precede or follow the diagnosis of IBD [214], and their activity can parallel intestinal inflammation or follow an independent course [201]. Gastroenterologists need to incorporate evidence originating from other fields to tailor the treatment for IBD patients with EIMs. Many IBD therapies (e.g. anti-TNF, anti-IL-23p19, anti-IL-23p40, JAK inhibitors, and S1P modulators) are also efficacious against immune-mediated EIMs and therefore can be used in coordinated management, as presented in Table 1. The gut-selective vedolizumab has not been studied in immune-mediated diseases other than IBD and showed inconsistent effectiveness for EIM control in observational studies [214]. IL-17 inhibitors are licensed for spondylarthritis, psoriasis, and psoriatic arthritis but contraindicated in IBD [215,216].

The most frequent EIM domain is joint involvement, which predominantly presents as spondylarthritis [217]. Spondylarthritis encompasses a spectrum of clinical entities with overlapping features and sometimes blurred distinctions. It usually includes axial spondylarthritis, psoriatic arthritis, arthritis related to IBD, reactive arthritis, and undifferentiated spondylarthritis. Axial spondylarthritis typically presents with inflammatory back pain, but can also involve the peripheral joints, entheses, or extra-articular districts [218]. It includes radiographic forms, based on the presence of radiologically identifiable sacroiliitis [219], and non-radiographic forms, although these are now considered part of a continuum [220]. Anti-TNF agents are recommended as the treatment of choice for patients with IBD and coexisting axial spondylarthritis, with the notable exception of etanercept – which should be avoided in this context, as it is ineffective for IBD and has been associated with potential disease exacerbation [221]. JAK inhibitors, despite having similar efficacy to that of anti-TNF agents, are reserved for patients that are unresponsive or ineligible for anti-TNF treatment [222]. Filgotinib is currently under evaluation for spondylarthritis [223]. In contrast, IL-23p19 [224] and IL-23p40 [225] inhibitors have shown no efficacy against axial spondylarthritis. Peripheral spondylarthritis is a group of conditions characterized by peripheral joint involvement (as opposed to axial spine or sacroiliac joint involvement). Peripheral arthritis in IBD can be classified into two entities: type 1 (pauciarticular), which is typically acute, asymmetrical, involves large joints such as the knee, and is usually self-limiting and related to IBD activity; and type 2 (polyarticular), which is symmetrical, predominantly affects small joints such as the metacarpophalangeal joints, follows an independent course from intestinal disease activity, and may

Table 1
Domain-based approach for the management of immune-mediated extra-intestinal manifestations in IBD. For refractory cases, consider combination therapies with or without anti-IL-17 antibodies on a case-by-case basis.

Domain	Treatment of choice	Second-line treatments	Adjuvant treatments
Joints: axial involvement	Anti-TNF[a]	JAK inhibitors[b]	NSAIDs (coxib)
Joints: peripheral involvement	Anti-TNF[a] Anti-IL-23p19[c] Anti-IL-23p40	JAK inhibitors	Methotrexate for CD, SASP for UC, steroids (local or systemic), NSAIDS (coxib), PDE4 inhibitors
Skin: psoriasis	Anti-IL-23p19[c]	Anti-TNF* Anti-IL-23p40 JAK inhibitors[b]	Steroids (local or systemic), PUVA
Skin: erythema nodosum	Anti-TNF[a]	Anti-IL-23p40 JAK inhibitors[b] (Anti-IL-23p19[c])	Steroids (local or systemic), NSAIDs (coxib)
Skin: pyoderma gangrenosum	Anti-TNF[a]	Anti-IL-23p40 JAK inhibitors[b] (Anti-IL-23p19[c])	Steroids (local or systemic), topical tacrolimus, conventional immunosuppressors
Eyes	Anti-TNF	Anti-IL-23p40 JAK inhibitors[b] (Anti-IL-23p19[c])	Steroids (local or systemic)

Coxib, cyclooxygenase-2 inhibitors; IL, interleukin; JAK, Janus kinase; NSAIDS, nonsteroidal anti-inflammatory drugs; PDE4, phosphodiesterase 4; PUVA, psoralen and ultraviolet-A; SASP, sulfasalazine, TNF, tumor necrosis factor.
[a] Infliximab and adalimumab for both CD and UC, golimumab for UC.
[b] Upadacitinib for both CD and UC, tofacitinib and filgotinib for UC.
[c] Mirikizumab not evaluated for psoriasis or psoriatic arthritis.

persist for years with the potential for articular erosion and destruction [226]. This distinction has practical clinical implications [226], as type 1 arthropathy may improve with effective control of the underlying intestinal inflammation, whereas type 2 arthropathy often requires targeted joint-directed therapy. Anti-TNF, anti-IL-23p19 and anti-IL-23p40 antibodies are all viable options for these conditions, with no clear preference in terms of efficacy on arthritis, while JAK inhibitors should be reserved for refractory or intolerant patients [227–229].

Psoriatic arthritis can be considered either a clinically heterogeneous subtype of spondylarthritis or part of a broader psoriatic disease spectrum. The GRAPPA guidelines endorse a domain-based approach targeting five clinical domains (each with distinct pathophysiological features requiring tailored therapy): peripheral arthritis, axial disease, enthesitis, dactylitis, and cutaneous/nail psoriasis [230]. Notably, psoriatic arthritis may present before, after, or independently of skin psoriasis [231]. Management of psoriatic arthritis with predominantly peripheral features mirrors that of peripheral spondylarthritis. For psoriatic arthritis with substantial axial disease, anti-TNF therapy is the first choice, followed by JAK inhibitors, while IL-23p19 and IL-23p40 inhibitors are not recommended due to lack of efficacy [229]. Of note, a post-hoc analysis of the DISCOVER-1 and -2 trials suggested that guselkumab improved axial symptoms in patients with psoriatic arthritis and imaging-confirmed sacroiliitis [232]; this finding deserves to be further explored.

Psoriasis, in its cutaneous form, includes plaque psoriasis (most common), inverse psoriasis, and nail pitting/onycholysis. Valid treatments for IBD patients with psoriasis include anti-TNF agents, IL-12/23 inhibitors, and anti-IL-23p19 (mirikizumab showed efficacy for psoriasis in an RCT [233] but is not approved for this indication and has not been evaluated in psoriatic arthritis) [230,234]. JAK inhibitors used for the treatment of IBD have not been formally evaluated in cutaneous psoriasis but have shown efficacy for improving psoriatic skin lesions in patients with psoriatic arthritis [235]. Current evidence suggests that anti-IL-17 anti-IL-23p19 agents have higher efficacy than other advanced therapies for the treatment of moderate-to-severe plaque psoriasis [236–238].

Erythema nodosum typically parallels intestinal disease activity, and remission can usually be achieved through effective control of the underlying intestinal inflammation [212]. In contrast, pyoderma gangrenosum may occur independently of intestinal activity [212]. Robust evidence supports the use of anti-TNF drugs [239,240] for pyoderma gangrenosum, and observational studies also indicate a potential benefit from ustekinumab and tofacitinib [241,242].

Finally, regarding the domain of the eyes, anterior uveitis in patients with IBD can be initially treated with topical corticosteroid eye drops, followed by systemic corticosteroids if the response is insufficient [243]. Anti-TNF agents have demonstrated efficacy in IBD-associated uveitis and should be considered in cases refractory to corticosteroid therapy [244–247] and can also be considered for refractory scleritis [248]. Observational data also support the effectiveness of ustekinumab and tofacitinib for the treatment of uveitis [241,249].

The management of paradoxical EIMs – where treatments induce immune-mediated manifestations they are intended to treat [250] - poses an additional challenge. Anti-TNF agents, despite being approved for the treatment of psoriasis, can induce or worsen psoriasiform skin lesions [251]. In these cases, when an anti-TNF antibody needs to be discontinued, evidence supports swapping to ustekinumab [201] – or, potentially, anti-IL23p19 agents. Vedolizumab, despite being a gut-selective anti-integrin antibody, has been linked to new-onset or worsening arthritis [252] and immune-mediated pneumonitis [253]. This association is possibly due to altered immune cell trafficking, leading to lymphocyte accumulation in the joints [254].

The presence of EIMs can inform other aspects of IBD management besides therapeutic choices. A notable example is primary sclerosing cholangitis, which is a chronic cholestatic liver disease that is often associated with UC and has a distinct pathogenesis from other EIMs [255]. IBD patients with this EIM face worse prognosis, with increased risk of hospitalization and mortality [256], a significantly elevated risk of colorectal cancer, which surpasses that of either disease alone [257,258]. Primary sclerosing cholangitis represents a critical modifier of disease trajectory in IBD: from a dynamic clinical profiling perspective, it necessitates personalized surveillance strategies and may influence both therapeutic prioritization and long-term management decisions. In this high-risk population, a tailored approach should include earlier step-up to advanced therapies, as well as endoscopic surveillance initiated at the time of diagnosis of primary sclerosing cholangitis, regardless of IBD duration [189].

7. Patients' needs and preferences

The definition and pursuit of optimal patient outcomes require the integration of evidence, clinical expertise, and the patient's perspective. Establishing a standard for (or against) a certain intervention requires an adequate understanding of both health and economic outcomes and a virtually unanimous consensus among patients regarding its desirability or undesirability [259]. Clearly, the management of IBD, where uncertainty often surrounds the real-world effectiveness of treatments and patients' perceptions of symptom burden vary widely, often lacks standards. Patient-centered care necessitates shared decision-making (SDM) [260], in which physicians present treatment options, benefits, and risks, while patients articulate their values, preferences, and concerns.

Research consistently shows that active patient participation in decision making improves treatment adherence and outcomes [261,262]. In a 2023 qualitative investigation, patients with IBD identified

prevention of surgery, sustained clinical remission, improved quality of life, reduction of urgency symptoms, and increased work productivity as the most meaningful treatment outcomes [263]. SDM is linked to greater patient satisfaction [264]. In one study, most patients expressed desires for active involvement and education about their disease and were more concerned about disease complications (especially surgery) than medication side effects [265]. Additionally, a 2023 RCT found that implementing an SDM tool increased combination therapy use among CD patients and reduced the number of patients receiving no treatment [266]. These results suggest that SDM may facilitate a more intensive treatment regimen, potentially leading to improved outcomes.

Key aspects of SDM in IBD (Fig. 5) include: 1) patient education about the disease course, risks of complications and disability, and treatment options; 2) discussion of the risk-benefit ratios of different therapies; 3) consideration of patient-reported outcomes beyond gastrointestinal symptoms, such as fatigue, work and social limitations, and negative effects on sexual activity and mental health; 4) treatment plans tailored to patients' evolving needs and preferences; and 5) effective communication, with clear language, sufficient time for reflection, encouragement of questions, integration of multidisciplinary perspectives, and acknowledgement of uncertainties.

Successful SDM requires understanding each patient's unique clinical and psychosocial contexts. Clinicians should explore patients' preferences regarding both their willingness to accept early interventions (versus a more conservative approach) and their preferred administration routes (intravenous, subcutaneous or oral). The practical impact of the disease and its treatment on daily activities, work, social interactions, and overall life satisfaction should be carefully addressed. Patients' priorities, including balancing symptom control and medication safety and minimizing healthcare visits, should be understood and respected. Holistic care should also consider emotional and psychological health, coping strategies and social support networks. Lastly, acknowledging the social determinants of health – including socioeconomic status, geographic accessibility to healthcare, and the stigma often associated with chronic gastrointestinal diseases – ensures truly equitable, patient-centered care.

Tailoring the medical management of special populations implies additional considerations. In pediatric cases, treatment goals also include healthy growth, attainment of developmental milestones, and reaching psychological maturity. Furthermore, the active involvement of parents or caregivers is essential, and structured planning for the transition from pediatric to adult care is critical to ensure continuity and adherence. As already stated, elderly and frail individuals necessitate careful consideration of age-related factors, including multimorbidity, polypharmacy, and increased susceptibility to adverse drug reactions and infections. Functional limitations, cognitive decline, reduced mobility, and the availability of caregiver support should all inform therapeutic decisions. People belonging to sexual and gender minorities may face additional barriers to care, such as stigmatization, implicit bias, or lack of provider awareness about specific health needs. In the context of chronic immune-mediated diseases, these individuals may have distinct psychosocial stressors – such as minority stress, internalized stigma, or lack of familial support – that affect both the disease trajectory and treatment compliance. Transgender and gender-diverse patients undergoing hormone therapy or gender-affirming surgeries may also require special consideration for drug interactions, altered

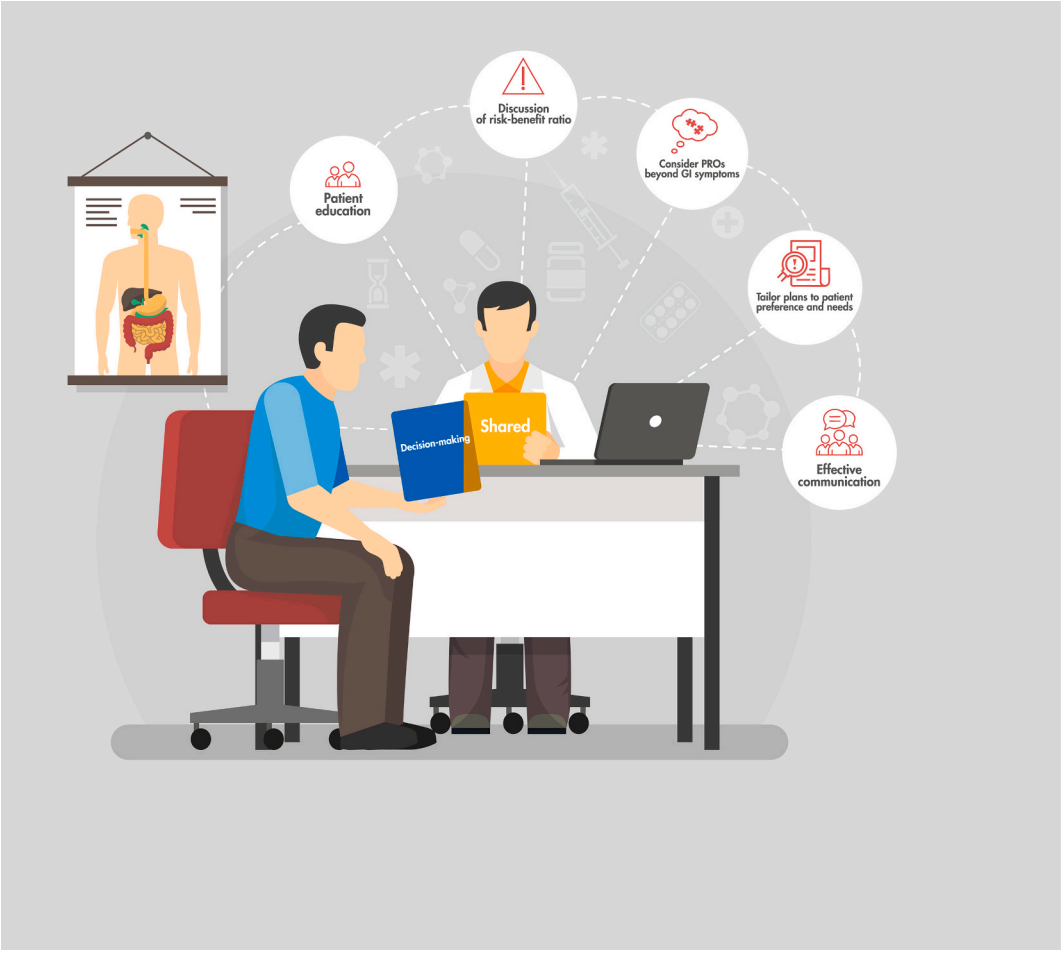

Fig. 5. Main aspects of shared decisionnmaking in IBD. GI, gastrointestinal; PROs, patient-reported outcomes.

pharmacokinetics, and tailored screening protocols. Inclusive communication and individualized care plans are vital to promoting equitable outcomes in this population.

Reproductive health in IBD patients is a key area for SDM, particularly regarding preconception counseling and pregnancy planning. Voluntary childlessness is more prevalent in women with IBD than in the general population [267] and is often due to misconceptions or anxiety surrounding fertility, pregnancy risks, and medication safety. Importantly, while IBD per se does not impair fertility [268], disease-related factors – such as active inflammation, perianal disease, some medications and prior abdominal or pelvic surgery – can reduce fertility [269]. The appropriate timing for pregnancy is crucial: IBD flares during the periconception period increase the risks of active disease during pregnancy and pregnancy complications [270], and female patients should be in stable remission for at least 6 months before seeking pregnancy [271]. Additionally, the choice of childbirth method should be determined through SDM, taking into consideration both obstetric- and IBD-specific factors.

Also important for reproductive health in IBD patients is treatment planning. Aminosalicylates, thiopurines, and therapeutic monoclonal antibodies are considered safe throughout conception, pregnancy and lactation, although data for vedolizumab and anti-IL-23 antibodies are limited; small molecule drugs cross the placenta and have teratogenic effects in animal models, although at serum concentrations significantly higher than those observed in humans [272]. Data on their safety in humans are emerging [269,272], and individualized risk-benefit assessments are essential. The planning of IBD surgery should also consider fertility preservation: ileal pouch-anal anastomosis (IPAA) reduces fertility [273], while procedures that avoid pelvic dissection do not [274]. Hence, deferral of IPAA formation until after childbearing can be proposed – when feasible – in women who desire future pregnancies. Caesarean delivery is more common in women with IBD than healthy controls [275–278], and it is recommended for patients with active perianal disease or IPAA, according to current guidelines [279].

Reproductive counseling for men with IBD should complement female-focused care. Male fertility, though often overlooked, can be negatively affected by active inflammation, malnutrition, and medications like sulfasalazine and methotrexate [280,281]. Thiopurines and most biologics have not demonstrated significant adverse effects on male fertility, while relevant data on small molecule drugs are limited [282,283].

8. Sustainability

We propose that therapeutic choices in IBD align with a principle of "double eco-sustainability", which we define as integrating both economic and ecological considerations (Fig. 6). In an era of rising healthcare costs and accelerating climate change, it is imperative to prioritize strategies that are not only clinically effective and cost-efficient but also environmentally responsible. The healthcare community has the opportunity – and responsibility – to lead the transition toward a greener, more sustainable model of chronic disease management.

Efficient resource allocation, particularly in a field marked by pronounced therapeutic heterogeneity, cannot disregard the principle of therapeutic appropriateness. Only by aligning treatments with the

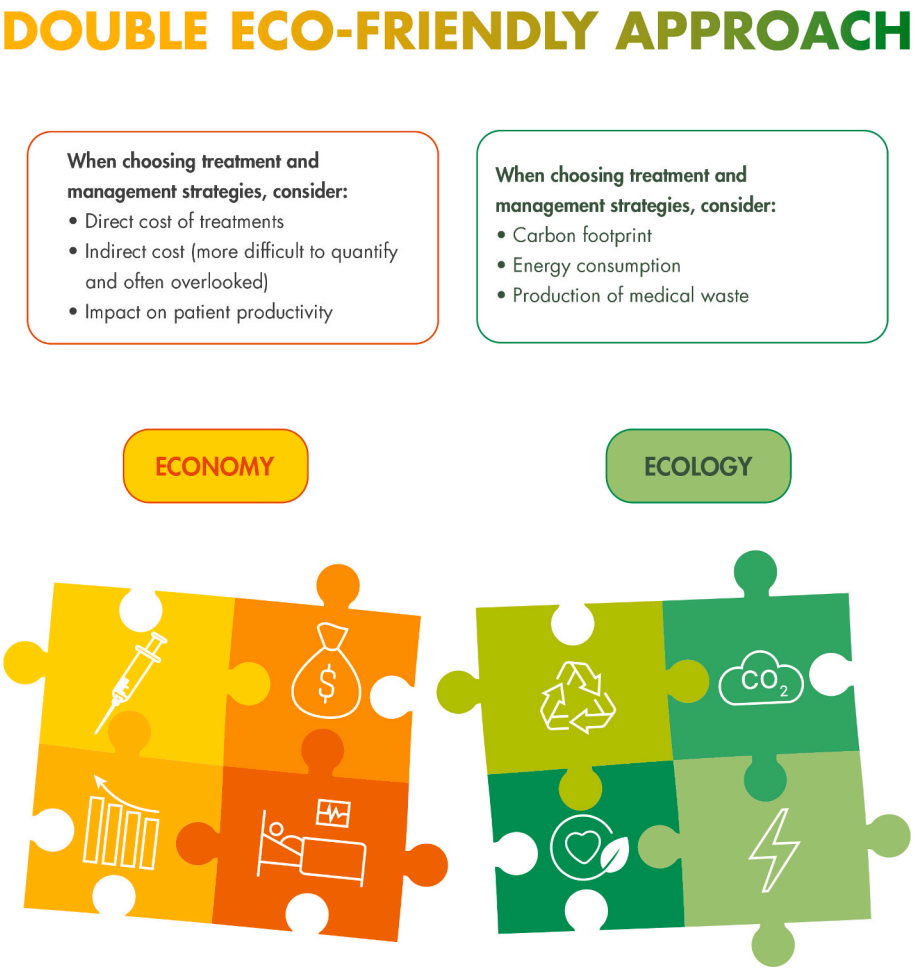

Fig. 6. Double eco-friendly approach to choosing treatments schedules in IBD: economic and ecological considerations.

individual patient's characteristics, expected response, and shared clinical priorities can we reduce waste, improve clinical outcomes, enhance quality of life, and ultimately generate meaningful value for the healthcare system. Appropriateness, in this sense, is not a restriction but a strategic driver for optimizing both clinical and economic impact.

The multidimensional clinical profiling of IBD patients, as outlined throughout this manifesto, is instrumental in enabling sustainability. Dynamic clinical profiling assesses not only clinical and molecular variables but also factors often excluded from conventional pharmacoeconomic analyses such as indirect costs (e.g. lost productivity, absenteeism) and intangible burdens (e.g. emotional distress, social impairment). By integrating these dimensions into healthcare, we can go beyond cost minimization and toward a more holistic, equitable framework for decision making, ultimately supporting a model of care that is sustainable in the broadest sense – economically, clinically, and socially.

8.1. *Pharmacoeconomics in IBD*

IBD care entails both direct and indirect costs. Direct healthcare costs, which are typically the concern of governments and private companies (e.g., private hospitals and healthcare insurances), include medication expenses as well as healthcare system expenditures for outpatient visits, hospitalizations, diagnostics and monitoring. Indirect costs, on the other hand, arise from the productivity loss of individuals and society and from the intangible consequences of a person's reduced ability to fulfil their potential. Although often considered separately, direct and indirect costs are tightly interconnected, and increased spending in one area may offset costs in another. For example, expensive but highly effective therapy may lower other direct costs, by reducing the need for hospitalization and surgery, and may also mitigate indirect costs. However, since indirect costs are challenging to quantify, they are frequently underestimated, leading decision makers to prioritize strategies that appear less costly in terms of drug prices alone [284].

Optimal resource allocation should take into account multiple factors, including monitoring strategies, the timing of advanced therapy initiation, and drug selection. Therefore, dedicated pharmacoeconomic analyses are needed to capture the true overall burden of IBD care. For instance, the early use of advanced therapies has the potential to achieve deep, sustained remission, thereby limiting complications and the need for surgery and hospitalization. Nonetheless, disparities in access persist, and uncertainty remains as to whether these therapies can truly modify the natural history of IBD. Biosimilars (which are biological medicines with highly similar molecular structure and no clinically meaningful differences compared to the originator product) have reshaped the cost curve in IBD, leading to substantial cost savings. Robust RCTs and real-world data support the clinical equivalence of biosimilars to the originator product and safe non-medical switching (i.e., switching stable patients to a biosimilar for pharmacoeconomic reasons) [285–288]. The interchangeability of these drugs is explained in policies of the US Food and Drug and Administration [289] and of the European Medicines Agency (for selected drugs) [290], and these policies facilitate the prescription of less expensive alternatives. Budget-impact analyses have shown large, durable savings when adalimumab and infliximab biosimilars are prescribed [291]. These saved funds can be reinvested to enable earlier biological drug initiation and sustained treat-to-target care. Emerging options such as subcutaneous infliximab also relieve infusion center overcrowding, further improving access [292].

8.2. *"Green" IBD*

Chronic diseases like IBD require lifelong monitoring and treatment. As their prevalence rises [187], so does their environmental footprint, which is driven by patient visits, diagnostic procedures and long-term therapies, all contributing to carbon emissions and medical waste [293]. Therefore, a more sustainable healthcare model is needed. In this section, we focus on the environmental implications of treatment decisions. Other relevant aspects, including the timing and type of procedures for diagnosis and monitoring, telemedicine, and the adoption of environmental-friendly medical disposables, have been extensively discussed elsewhere [293]. In this regard, the appropriateness of medical procedures warrants careful consideration. Unnecessary endoscopic procedures, redundant investigations, and overly intensive monitoring protocols contribute significantly to healthcare-related carbon emissions and resource overuse. Integrating principles of appropriateness into dynamic clinical profiling may enable a more rational, patient-centered allocation of endoscopic and imaging resources. When aligned with disease activity and patient risk, this approach can optimize resource utilization and promote more sustainable care without compromising clinical outcomes.

Drug selection is key in reducing healthcare's ecological footprint. Subcutaneous formulations of biologics may offer significant ecological advantages over intravenous formulations, although some differences between subcutaneous therapies may exist depending on the specific device used. Subcutaneous therapies require fewer hospital visits, thereby reducing transport-related emissions, and reduce the use of single-use plastics (e.g. intravenous bags and tubing) [294]. Notably, both infliximab [295] and vedolizumab [296] are now available as subcutaneous formulations, which have demonstrated non-inferiority to their intravenous counterparts. The availability of biosimilars introduces another opportunity: these drugs not only lower healthcare costs but also involve lower resource use during production compared to originator biologics [293]. The manufacturing of oral small molecule drugs consumes 10–100 times less water than that of biologics [297]. Moreover, these drugs do not require a hospital visit for administration, hence their use reduces the patient's carbon footprint. Finally, to reduce the reliance on high-resource drugs while also improving patient outcomes, physicians should consider prescribing adjunctive therapies with documented efficacy, such as the plant-derived compounds curcumin and Qing Dai [298,299] or targeted dietary interventions [300].

Dosing regimens also have substantial environmental implications, so optimized regimens with minimized environmental burden should be preferred. For instance, infliximab optimization to 10 mg/kg every 8 weeks, rather than 5 mg/kg every 4 weeks, decreases infusion frequency and associated waste and was shown in a multicenter retrospective study to maintain comparable effectiveness [301]. For other parenteral drugs, interval shortening is the standard approach for optimization, but dose escalation may be equally effective in some cases: Notably, adalimumab optimization to 80 mg every 2 weeks had comparable effectiveness [302] and pharmacokinetics [303] to the 40 mg weekly regimen. From an ecological perspective, evaluating whether a dose increase is equally effective to interval shortening for other biologics could help identify optimization strategies that achieve clinical goals with a reduced environmental footprint. Additionally, therapeutic drug monitoring may help identify patients suitable for dose de-escalation. For example, it has been shown to be useful in identifying patients who maintain remission at lower levels of infliximab [304] and adalimumab [305], thereby allowing for dose reduction and fewer administrations. From a more general standpoint, closer attention to de-escalation and treatment exit strategies is warranted, not only to reduce overtreatment, but also to significantly lessen the environmental impact of prolonged therapies.

9. Incorporating dynamic clinical profiling into decision making

Optimal decision making in IBD requires the integration of the five domains presented here to establish priorities for individual patients. Fig. 7 provides a conceptual framework to support clinical decision making in IBD, integrating these five domains. The nuances of decision making cannot be fully captured in written format, but illustrative scenarios help clarify how specific domains can guide therapeutic choices.

Generally, evidence for the most efficient profiling method is scarce.

Fig. 7. Framework for the dynamic medical profiling of IBD patients and key considerations for domain-based clinical decision making. EIMs, extraintestinal manifestations; IL, interleukin; JAK, Janus kinase; S1P, sphingosine-1-phosphate; TB, tuberculosis; TNF, tumor necrosis factor; CV, cardiovascular; VTE, venous thromboembolism.

This is because RCTs are usually designed to assess differences between the investigated product and placebo or comparator products. Little effort has been dedicated to profile patients or to compare drugs in different clinical scenarios. Hence, recommendations on which drug to use in special situations are based mainly on indirect evidence, real-world experience, or expert opinion.

A severity-based approach presents challenges. The most robust data on this approach are limited to prior anti-TNF exposure, and clinical evidence consistently shows that treatment response differs significantly based on exposure status. Translational research found that T cells overexpressing the IL-23 receptor are resistant to anti-TNF-induced apoptosis [40], highlighting a potential mechanistic basis for the superiority of IL-23 inhibitors in this setting. Other factors influencing IBD complexity are harder to quantify and are often incorporated into the clinician's overall assessment, but their implications for therapeutic decisions are not definitively established.

For drug-naïve patients with UC or luminal CD, infliximab biosimilars are generally preferred, especially in more severe cases; adalimumab remains a valid alternative in CD with an efficacy comparable to that of infliximab [306], while it is less suitable as first-line therapy in UC. An anti-TNF agent in combination with a thiopurine (for 6–12 months) should be considered due to the beneficial effects on pharmacokinetics, with stronger evidence for infliximab [58,59,307]. S1P receptor modulators demonstrated significantly higher efficacy in drug-naïve patients and can be considered a valid alternative to anti-TNF antibodies in this population, even though comparative safety and efficacy data are currently lacking. Vedolizumab is better suited for first-line use in UC, but it has higher direct costs than anti-TNF biosimilars. Anti-IL-23 agents are emerging as viable options for both CD and UC, particularly with the anticipated availability of ustekinumab biosimilars. Currently, regulatory restrictions limit the use of JAK inhibitors as first-line agents (despite evidence supporting their efficacy), so here

they are considered only as second-line drugs.

In anti-TNF-exposed patients with UC, either JAK inhibitors or anti-IL-23 agents can be considered, with vedolizumab less preferred due to its known lower efficacy in exposed patients. In anti-TNF-exposed patients with CD, upadacitinib and anti-IL-23p19 agents can be considered, while ustekinumab and vedolizumab appear to be less effective. Patients with multidrug-refractory disease may benefit from advanced combination therapy [308], whose effectiveness in this patient population is supported by observational reports [309,310]. Nonetheless, the optimal therapeutic regimen is unknown, and more safety data are needed before advanced combination therapy can be considered a standard choice.

In perianal CD, anti-TNF agents have the strongest evidence for efficacy, possibly with a preference of infliximab over adalimumab. While evidence supporting combination therapy with thiopurines is limited, the known pharmacokinetic benefits justify its consideration, considering the reported association between higher trough levels and better outcomes in these patients. The use of other therapies is supported by data mainly from observational studies or post-hoc trial analyses and should be reserved for patients who are refractory to or intolerant of anti-TNF drugs. Of note, ongoing placebo-controlled studies are evaluating the efficacy of ustekinumab [311] and guselkumab [312] in patients with perianal CD.

The optimal management of POR remains debated. Early endoscopic evaluation (ideally within 6–8 months of surgery) is crucial for guiding step-up therapy, although intestinal ultrasound and fecal calprotectin testing may soon become valid, non-invasive alternatives. Patients at highest risk for POR may benefit more from early prophylaxis than from an endoscopy-driven approach. However, the optimal risk threshold for initiating prophylaxis is not clear, so the decision-making process should be guided by a holistic assessment incorporating disease severity and patients' preferences rather than by an exact computation of risk factors. Anti-TNF agents and vedolizumab have the strongest evidence for POR prevention, with no clear efficacy difference between them. Evidence supporting the use of other drugs is more limited, and they should be reserved for patients who fail or cannot tolerate these therapies.

Validated frailty- and disability-specific metrics should be considered for screening in all patients with IBD, as these assessments may help guide treatment selection. For frail patients, vedolizumab or anti-IL-23 drugs may be preferred due to their favorable safety profiles. Achieving adequate control of intestinal inflammation must be factored into the risk-benefit analysis. When the safer options are not available (such as in patients who have already failed them), prioritizing disease control can sometimes be an adequate choice, as reducing inflammatory burden can mitigate frailty. Non-immune comorbidities can further guide therapy selection. Anti-TNF agents are contraindicated by class III or IV heart failure and should not be used in patients with chronic obstructive pulmonary disease. JAK inhibitors, on the other hand, should be avoided in patients at high risk of cardiovascular events including VTE. Optimal management should also include risk-mitigation strategies, such as timely, appropriate vaccination [313] to allow for the safe administration of effective therapies. For example, live attenuated vaccines can be administered before advanced therapy, and pneumococcal and zoster vaccination can be done in high-risk populations. Patients unfit or unwilling to get vaccinated deserve even further caution.

Mirroring the domain-based approach endorsed by GRAPPA [230], a similar strategy can be applied to IBD-associated EIMs. For axial joint involvement, first-line therapy should consist of an anti-TNF agent. For patients with peripheral joint involvement, anti-TNF, anti-IL-23p19, and anti-IL-23p40 antibodies are all valid first-line options. JAK inhibitors should be considered for patients with axial or peripheral spondylarthritis who are unresponsive to or intolerant of other drugs. For patients with cutaneous psoriasis, evidence supports the use of an anti-IL-23p19 agent as the first-line therapy. Ustekinumab and anti-TNF therapies can be considered as second-line treatment. JAK inhibitors, although not officially approved for plaque psoriasis, have demonstrated efficacy and can therefore be a valid option in this context. Finally, in patients with scleritis or uveitis, an anti-TNF agent is the preferred choice. Anti-IL-17 agents, although approved for spondylarthritis and psoriasis, should be avoided in IBD due to their association with disease exacerbation. However, for drug-refractory EIMs, they may be considered in combination with IBD-directed therapies. Vedolizumab may be particularly useful due to its favorable safety profile, while the rationale for blocking IL-23 (which is upstream in the same inflammatory pathway) may be questionable. The evidence supporting the effectiveness and safety of combination therapies is limited, so their use should be reserved for selected, suitable patients.

When a physician considers initiating an advanced therapy, ensuring the engagement of the patient in this decision-making process is crucial. Discussions should center on therapeutic goals, expectations, and preferences, particularly in cases where efficacy, safety, comorbidities, or EIMs do not distinctly favor one treatment over another. In this context, while pharmacoeconomic evaluations are important, they should take a backseat to the management needs of complex patients. It is essential to address pharmacoeconomic factors, extending beyond drug costs to include indirect costs and cost-effectiveness/opportunity analyses. In the absence of robust data, cost-effective options for direct costs should be prioritized, with an additional focus on ecological sustainability.

10. Conclusions

Despite the increasing availability of novel treatments, the therapeutic ceiling in IBD remains stubbornly intact. The development of new drugs is essential, but the past decade has irrefutably demonstrated that drug innovation alone is insufficient. The relentless heterogeneity of IBD shatters the hope that a panacea will eventually arrive and underscores the need to fully leverage every tool in our arsenal. When a painting appears flawed, do we blame the brush or the hand that wields it? Just as painters need to refine their craft, so too must we, as physicians, sharpen our therapeutic approach, by aligning drug mechanisms with the underlying biology, timing interventions to disease course, and tailoring treatments to the individual before us.

Crucially, the clinical profiling of patients must evolve into a holistic, dynamic process that recognizes that both patients and their disease are not static and that is incorporated in the treat-to-target approach. The definition of treatment success may differ from patient to patient and from time to time, and therapeutic strategies need to be optimized to achieve the goals we set. Furthermore, advancing molecular precision medicine is key: reliable biomarkers should be identified, and clinical profiling systems should be developed to anticipate the efficacy of specific treatment strategies and to ensure that the right intervention reaches the right patient at the right time. This will require a commitment to the continual reassessment of disease characteristics and patient needs. We need dynamic patient profiling that characterizes specific molecular signatures associated with a certain moment of disease and that enables us to set the most appropriate therapeutic targets for a specific patient and to identify the best strategies to pursue them. The next era of IBD management will require more than just new drugs. It will demand a paradigm shift in how we think about disease, treatment, and patient experiences.

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