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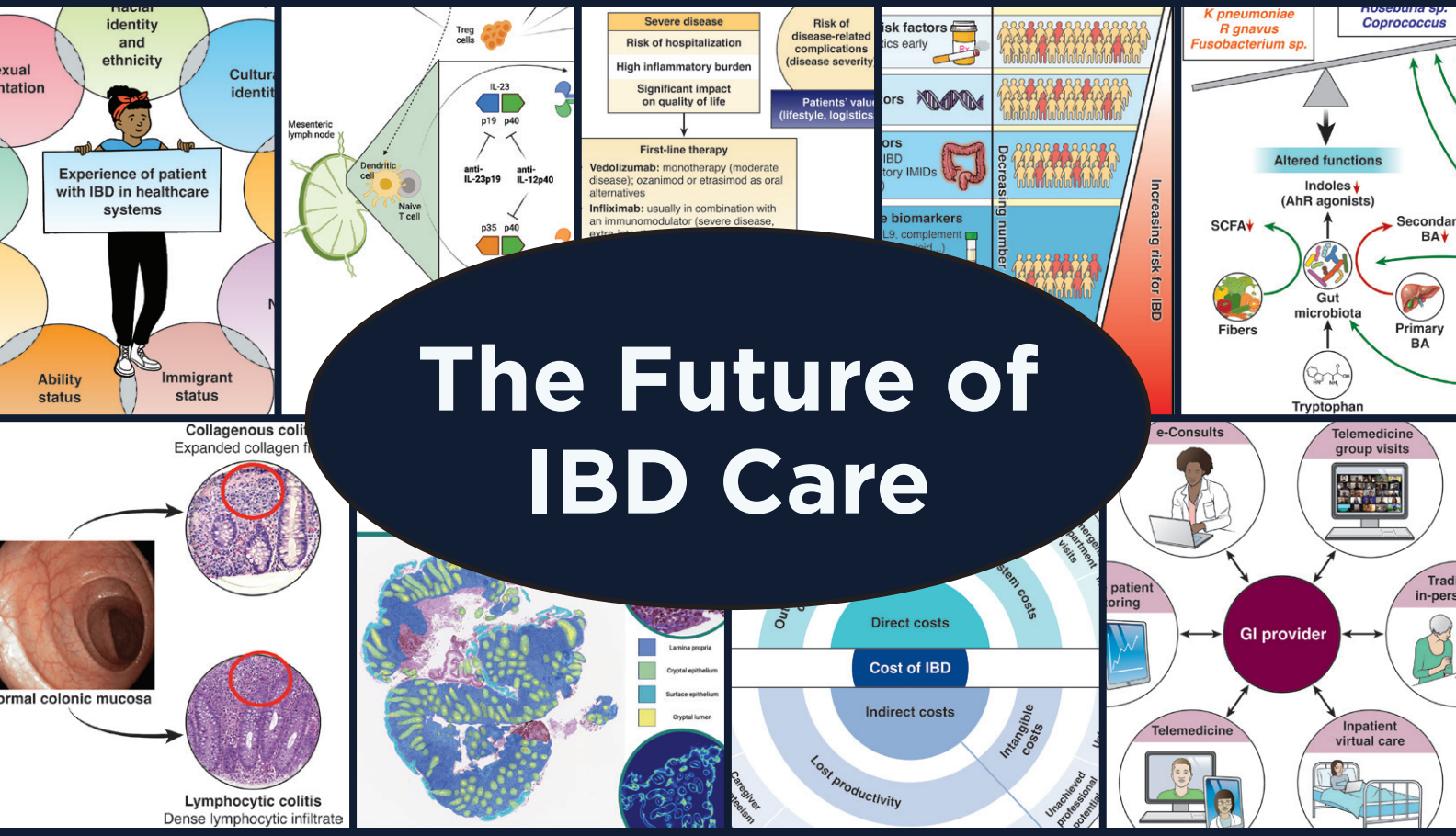

The Future of IBD Care

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ON THE COVER

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INTRODUCTION

The Future of Inflammatory Bowel Disease Care





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As we approach the 100th anniversary of the description of Crohn's disease,[1] the advances in the management of inflammatory bowel disease (IBD) have been remarkable. Significant progress in the understanding of the pathophysiology of IBD has led to development of advanced therapies, such as biologics, small molecules, and more personalized treatment strategies. These innovations have transformed the landscape of IBD care, improving patient outcomes, reducing complications, and enhancing overall quality of life. However, despite these impressive strides, challenges remain, including the rising incidence of IBD worldwide, the financial burden of disease, and the therapeutic ceiling reached, highlighting the need for newer paradigms, new trial designs, and new strategies. With a continuous surge of evidence from real-world studies and randomized clinical trials, health care providers face challenges in keeping up with the data. In this special issue of *Clinical Gastroenterology and Hepatology*, we have enlisted the help of experts to summarize recent advances and speculate on the future of IBD care, highlighting the need for continued research and innovative solutions for this complex and disabling disease.

As the prevalence of IBD continues to increase, the rising costs of caring for these patients will represent an extraordinary burden for developed and developing nations. Burisch, Claytor, Hernandez, Hou, and Kaplan review the magnitude of direct medical costs for Crohn's disease and ulcerative colitis (eg, costs of biologics and advanced therapies, hospitalizations, surgeries) and remind us about the indirect costs of these illnesses (eg, missing work, delayed entry into or early exit from workforce, caregiving costs).[2] The authors identify challenges in controlling costs and offer strategies to make the care of patients with IBD more cost-effective, with a particular focus on the use of biosimilars and the use of multidisciplinary teams, telemedicine, and technology to reduce the need for emergency department visits and hospitalizations.

The rising incidence of IBD in areas undergoing fast modernization highlights the role of environmental triggers to disease onset and represents a call to action for IBD prevention. What if we could either modify our environment to reduce exposure to factors that promote inflammation or monitor high-risk individuals, such as first-degree relatives of patients with IBD? In the second article, Lopes, Turpin, Croitoru, Colombel, and Torres review potential biomarkers of future IBD risk and propose risk-stratification methods to identify those at the highest risk for developing IBD.[3] They suggest interventions that may lower risk, including lifestyle modifications, dietary interventions, microbiome-targeted strategies, and perhaps using advanced therapies in persons at highest risk. They also review potential challenges to these preventive strategies.

Many of us suspect that "all roads lead through the microbiome" when discussing risk factors for IBD, and patients and providers want to know if a special diet can lead to mitigation or even remission of these conditions. In the third article, Ananthakrishnan, Whelan, Allegretti, and Sokol review the evidence for the role of the microbiome and diet in the development of IBD and

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discuss multiple potential interventions in the form of prebiotics, probiotics, fecal microbial transplantation, and diet.[4] The evidence for the relationship between diet and both onset of IBD and worsening disease course are nicely summarized. The authors review specific dietary interventions, such as exclusive enteral nutrition, the Crohn's Disease Exclusion Diet, and other therapeutic diets. Finally, they identify challenges and opportunities in implementing such strategies in an effective manner.

Seasoned clinicians know that managing patients with IBD is not just about managing gastrointestinal symptoms and issues. IBD has profound effects on quality of life and mental health and bidirectional relationships with social determinants of health, diet, and sleep. In addition, certain aspects of health maintenance, such as immunization recommendations, need to be comanaged by health care providers caring for patients with IBD. Click, Cross, Regueiro, and Keefer present the spectrum of holistic, patient-centric IBD care, and also provide updates on virtual care, the adoption of which has certainly accelerated during the COVID-19 pandemic.[5] Telehealth encompasses e-consultations, remote monitoring, virtual visits, and in the future perhaps even virtual inpatient care. With the rising burden of IBD and increasing number of patients visiting our clinics, such alternative models of care need to be better explored.

Although "artificial intelligence" at some level is a kind of buzzword, it is here to stay and will increasingly occupy a portion of the gastroenterologist's care, including in endoscopy, documentation, diagnosis, clinical trial recruitment, and even drug discovery. Silverman, Shung, Stidham, Kochhar, and Iacucci present what is available and what is emerging in the fast-moving artificial intelligence field for IBD.[6] This includes the use of large language models, assistance with endoscopy identification (eg, dysplastic lesions, disease severity), development of new indices for disease activity, assistance with histologic scoring, assistance with radiologic assessment, and identification of high-risk patients.

Just as we recognize that our "average IBD patient" from 30 years ago looks totally different than now because of the global spread of IBD, we must be sensitive to the various cultural, racial, ethnic, socioeconomic, and sexual orientation differences among our patients. Chedid, Targownik, Damas, and Balzora provide a comprehensive update on what it means to provide culturally sensitive care to and to practice cultural humility with historically disadvantaged groups, such as Blacks, Hispanics, and those with LGBTQ+ identity.[7] Importantly, they propose solutions to historical disparities in care, such as training health care professionals in empathy and cultural respect, diversifying the health care provider workforce, and improving representation of historically disadvantaged persons in IBD research.

In some ways we have "an embarrassment of riches" with respect to the range of medical therapies now available for patients with IBD. Although this is obviously a plus for patients and providers, it can be overwhelming to decide about the appropriate next therapy for a given patient. Fudman, McConnell, Ha, and Singh review important clinical aspects of the 3 classes of medications that have become clinically available over the past 5 years: Janus kinase inhibitors, anti-interleukin-23 antagonists, and sphingosine-1-phosphate receptor modulators.[8] The authors also provide a view on how to position all of our medical therapies in patients with Crohn's disease and ulcerative colitis, including cost and access considerations.

In recent years, clinicians have increasingly combined biologics and/or advanced small molecules in some of our more medically refractory patients with IBD, but this has not necessarily been done in a systematic way. Battat, Chang, Loftus, and Sands review the conceptual frameworks, both pharmacologic and temporal, for combined advanced targeted therapy in IBD; review evidence supporting the use of combination therapy in other fields, such as oncology, infectious diseases, and rheumatology; and appraise the evidence supporting use of combined therapies in IBD.[9] They also provide a general approach for combined advanced targeted therapy in refractory patients and those with either extraintestinal manifestations or with associated immune-mediated inflammatory diseases. Finally, they speculate on the future of combined advanced targeted therapy in IBD including newer mechanisms of action.

As our patients with IBD become more complicated, so does clinical trial design. Ma, Solitano, Danese, and Jairath provide a comprehensive update on innovative changes in early phase clinical trial design, including exposure-driven pharmacokinetics, proof of target engagement, reducing exposure to placebo using historical data, Bayesian approaches, and the use of platform or basket trial designs.[10] Late-phase trial design innovations include the use of extended induction for nonresponders, a return to "treat-through" trial designs, and early corticosteroid tapering. The advent of head-to-head biologic trials and trials of treatment strategies rather than individual medications has helped providers better position medications.

In some ways, collagenous colitis and lymphocytic colitis are the "red-headed stepchildren" of conventional IBD, and at times less well-studied, because long-term outcomes are generally favorable. However, their impact on patients' quality of life is considerable. Peery, Khalili, Münch, and Pardi review the epidemiology, clinical presentation, diagnosis, natural history, pathogenesis, and conventional medical therapy of microscopic colitis.[11] Importantly, they also provide an update on the evidence to support the use of advanced therapies, such as immunomodulators, biologics, and small molecules in patients with refractory microscopic colitis.

In summary, in this special issue, we explore a wide array of topics that are critical to the evolving landscape of IBD care, from financial sustainability of IBD care, to disease prevention, combination therapies, special

populations, incorporation of new technologies, and new trial design. As we continue to deepen our understanding of IBD, these discussions pave the way for a more effective, accessible, and patient-centered approach, ensuring that the progress of today translates into better outcomes for patients tomorrow. We hope that you will find this special issue informative and helpful.

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Conflicts of interest

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REVIEW ARTICLES

The Cost of Inflammatory Bowel Disease Care: How to Make it Sustainable

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The rising global prevalence of inflammatory bowel diseases (IBDs), such as Crohn's disease and ulcerative colitis, underscores the need to examine current and future IBD care costs. Direct health care expenses, including ambulatory visits, hospitalizations, and medications, are substantial, averaging $9,000 to $12,000 per person annually in high-income regions. However, these estimates do not fully account for factors such as disease severity, accessibility, and variability in health care infrastructure among regions. Indirect costs, predominantly stemming from loss in productivity due to absenteeism, presenteeism, and other intangible costs, further contribute to the financial burden of IBD. Despite efforts to quantify indirect costs, many aspects remain poorly understood, leading to an underestimation of their actual impact. Challenges to achieving cost sustainability include disparities in access, treatment affordability, and the absence of standardized cost-effective care guidelines. Strategies for making IBD care sustainable include early implementation of biologic therapies, focusing on cost-effectiveness in settings with limited resources, and promoting the uptake of biosimilars to reduce direct costs. Multidisciplinary care teams leveraging technology and patient-reported outcomes also hold promise in reducing both direct and indirect costs associated with IBD. Addressing the increasing financial burden of IBD requires a comprehensive approach that tackles disparities, enhances access to cost-effective therapeutics, and promotes collaborative efforts across health care systems. Embracing innovative strategies can pave the way for personalized, cost-effective care accessible to all individuals with IBD, ensuring better outcomes and sustainability.

Keywords: Crohn's Disease; Inflammatory Bowel Diseases (IBD); Ulcerative Colitis.

Inflammatory bowel diseases (IBD) (Crohn's disease [CD] and ulcerative colitis [UC]), affect approximately 7 million people globally.[1] The prevalence of IBD is steadily climbing, approaching 1% in certain industrialized regions, including Europe and North America, within the next decade.[2,3] More patients living with IBD, combined with continuing innovations in IBD therapeutics, diagnostics, and preventative strategies, will inevitably require escalating health care resources. The widening landscape of effectivebiologic and small molecule agents has shifted IBD management toward early, aggressive treatment and treat-to-target approaches.[4,5] These trends place increasing burdens on health care systems and require the development of strategies that ensure the equitable, affordable, and sustainable delivery of IBD care. Herein, we describe the current and future projections of costs of IBD care and discuss measures to foster sustainability and cost reduction.

Current Landscape of IBD Care Costs – The Drivers

Direct Health Care Costs of IBD

Direct health care costs of IBD include ambulatory visits to primary care, specialists (eg, gastroenterologists) and allied health care professionals (eg, dieticians), visits to the emergency department, admissions for hospitalization or surgery, diagnostic investigations (laboratory, radiologic, endoscopy), ancillary products (eg, ostomy appliances, complimentary therapy), and medications[6–8] (Figure 1).

Abbreviations used in this paper: **CD, Crohn's disease; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UC, ulcerative colitis; U.S., United States; VHA, Veterans Health Administration.**

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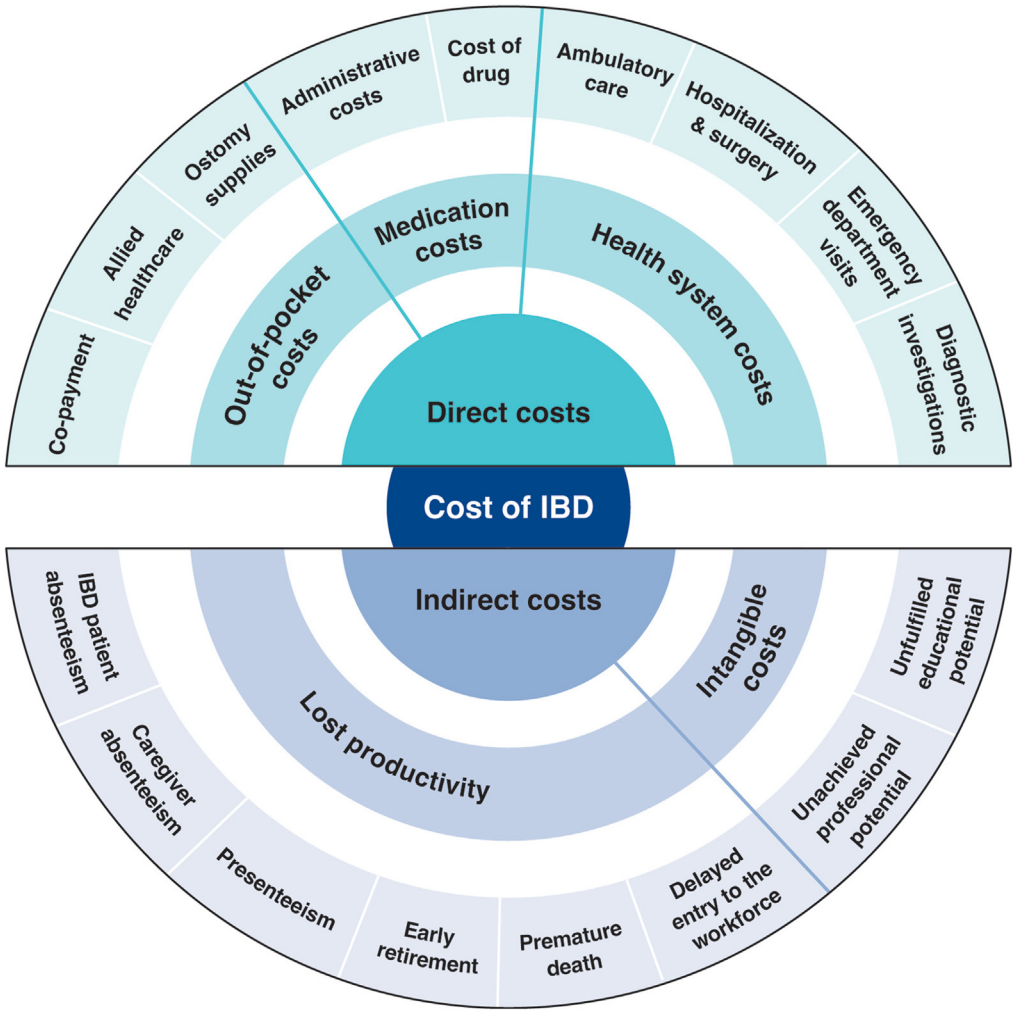

Figure 1. Overall cost of IBD care based on domains of direct and indirect costs. *Allied health care: encompasses a diverse range of specialized professions (ie, dieticians, physical therapists) that collaborate with medical professionals to deliver diagnostic, therapeutic, and support services in patient care.

The *Lancet Gastroenterology & Hepatology* Commission was an international effort to summarize the cost of IBD in high-income regions.[6] The commission estimated that the mean annual direct per person health care cost in 2021 USD was $12,000 for CC and $9,000 for UC.[6] These estimates do not even include disease duration (ie, first years of treatment are typically more expensive than later years), disease severity and phenotypic differences (ie, a small percentage of patients contribute disproportionately to overall health care expenditures),[9] accessibility, penetration, pricing of expensive advanced therapies, or variability in health care infrastructure among regions. Most published studies estimate IBD cost in the era after anti-tumor necrosis factor (TNF) entry, with limited data accounting for increased costs of newer advanced therapies or decreased costs of biosimilars.[6,7]

The per-person annual estimates multiplied by local prevalence data govern annual budget impact analyses per region. For example, the most recent data from the United States (U.S.) estimated that the prevalence of IBD was 0.7% of the population, representing 2.39 million individuals living with IBD.[10] Using the Cost Commission annual average, the annual cost of IBD in the U.S. approximates $50 billion. Regions with specific mean annual estimates can compare their cost with the baseline average from the collective data of high-income settings derived from the Cost Commission. For example, the Crohn's and Colitis Canada 2023 IBD Impact report[11] calculated that the average annual per person cost of IBD in Canada was $10,336 CDN, which translates into a total cost of $3.3 billion CDN,[3,7] given the estimated prevalence of 0.8% (or 330,000 Canadians).

Although variability in annual mean cost was noted in each study, all studies demonstrated a shift over time from costs associated with hospitalizations to costs of medications.[6] In the pre-biologic era, hospitalizations and particularly surgery accounted for more than 50% of direct health care costs of IBD. For example, a population-based inception cohort of patients with IBD in the pre-biologic era in Western European countries and Israel (1993–2004) estimated an annual average cost of IBD of €1,871 per patient, with 53% attributable to hospitalizations.[12] In the pre-biologic era, over 60% of IBD-related costs in the U.S. were related to emergency department visits and hospitalizations, up to $25 billion

annually of direct costs. In 2008, between 27% and 35% of costs were attributed to medications, predominantly 5-ASAs.[13]

Contemporary studies show that the increased penetration of anti-TNF therapies has raised costs of IBD care overall, driven by medication costs.[6] An updated European inception cohort (2010–2015) showed that 75% of patients with CD and 50% of patients with UC were prescribed biologic therapy within 5 years of diagnosis.[14] In Manitoba, the direct health care cost of IBD more than doubled from $3,354 CDN per person per year in 2005 to $7,801 in 2015, largely driven by increased use of anti-TNF therapies.[15] In 2005, 48% of spending was driven by hospitalizations and 34% by medications, compared with 22% and 65% for hospitalizations and medications in 2015, respectively.[15] Recently, costs of administering medications are shifting, with subcutaneous treatments drawing patients from infusion clinics to home-based care. Unfortunately, although home-based infusions reduce infusion-related costs, insurance claims data did not show any significant cost savings with this strategy.[16]

The costs of prescription drugs for IBD vary significantly worldwide, influenced by government regulation of prices and dynamics in the biosimilar market. A particular outlier among high-income countries is the U.S., where manufacturers set prices freely. The lack of nationwide price regulation, coupled with the fragmentation of the U.S. health care system and prolonged market exclusivity periods, result in U.S. drug prices that exceed, on average, international prices by several-fold. With no government negotiation or regulation of drug prices until the recent Inflation Reduction Act, private insurers are left to negotiate directly with pharmaceutical manufacturers via confidential discounts, also known as rebates, which increase opacity in the drug supply chain.[17] Even when insurers are successful at negotiating discounts, patients seldom benefit, as cost-sharing paid at the point-of-sale is based on the full, non-discounted price.[18]

Both hospitalization and surgical rates have decreased over the past 20 years.[19–21] Effective biologic therapies, dysplasia surveillance, and outpatient *Clostridioides difficile* regimens have reduced hospital-related charges.[19,22] Unfortunately, the costs of IBD-related hospitalizations have not fallen as dramatically in the same time span, each costing more today than a decade ago. The biologic era is marked by more complex patients admitted with greater disease severity (eg, medically refractory to biologics, requiring novel agents), decreased access to high-quality care (eg, underserviced area of residence), older age, and a greater burden of comorbidities. Additionally, cost for in-patient care has risen disproportionately to inflation, primarily due to charge inflation in the U.S.[23] Collectively, the rising expense of hospitalization has blunted the cost savings of lower rates of admission. Furthermore, costs may continue to escalate as patients are cycled through multiple ineffective medications, particularly those refractory to biologics, who may require novel agents or dual targeted therapy at higher rates. Although specific interventions, such as early laparoscopic ileocecal resection, may offer cost-effectiveness advantages over treatments like infliximab for ileitis,[24] the overall trend suggests a persistent challenge in managing health care expenses amid evolving treatment landscapes.

Direct health care costs are often viewed separately, paid for by different companies and individuals. However, all costs borne to society are intertwined (Figure 1). The challenge of intertwined costs is that one payer may need to spend more for another payer to save even more. Money spent on drugs that increase direct health care costs are offset in part by lower health care expenditures from reduced hospitalizations and surgeries. Moreover, direct health care expenditures need to be viewed through a lens of indirect costs to an individual and society.

Indirect Costs of IBD

Indirect costs are those attributed to an individual with IBD or society as a whole, stemming from the disease limiting the full potential of a person's contribution to oneself or society.[8,25] Indirect costs of IBD predominantly manifest as loss in productivity, as defined by absenteeism (ie, lost wages from missing work), presenteeism (ie, reduced capacity at work), early retirement, premature death, delayed workforce entry, and other intangible costs (not achieving maximal educational or professional accomplishments).[8,25] Indirect costs do not represent money spent by the health system to care for IBD or by the individual with IBD; rather, these costs are lost by the individual or society (Figure 1).

Measurement of indirect costs is abstract, with less published data available and less comprehensive metrics (ie, limiting domains to "absenteeism" or "presenteeism"). In 2023, the Crohn's and Colitis Canada estimated that the indirect cost of IBD in Canada was $1.51 billion CDN based on absenteeism, presenteeism, unemployment, premature death, and caregiving costs.[25] The cost of absenteeism was based on a survey that showed Canadians with IBD missed more than 4.4 days per year as compared with working age adults without IBD.[26] The excess loss of work was estimated to cost $1,080 annually per working-age adult with IBD. In Canada, approximately 150,000 adults were determined to be employed with IBD in 2023,[3] leading to a budget impact analysis of $163 million lost annually to absenteeism.[26]

A national Swedish study used disability pension and sick leave to define the cost of loss of productivity, which estimated that employable adults with IBD cost society on average $22,000 and $14,000 USD in 2020 for CD and UC, respectively.[27] Among children with IBD, absenteeism in their caregivers was estimated to be €6,272 (2021) in the first year of diagnosis.[28] Presenteeism, or working but not at full capacity, has been poorly studied,

with one study from Finland estimating the cost at €640 per year per patient.[29]

Despite these studies, many aspects of indirect costs to individuals with IBD and society are largely unknown, which ultimately results in an underestimation of the actual indirect costs of IBD. For instance, a young individual with IBD may not achieve their full potential by altering their education, delaying their entry into the workforce, or not achieving their career trajectory. Placing a dollar value on loss of aspirational accomplishment is critical, though inherently unquantifiable.

Challenges in Achieving Cost Sustainability: Disparities, Access, and Affordability

Clearly, cost sustainability in IBD health care is a complex goal, challenged by disparities in access to care and treatment affordability, limited access to cost-effective treatment options, and lack of standardized guidelines for cost-effective care delivery. Additionally, underinsurance can significantly impact the quality of care and lead to difficulties in affording necessary treatments.[30] These obstacles to achieving cost sustainability perpetuate inequalities in health care utilization and outcomes.

IBD is increasing in incidence among racial and ethnic minorities globally.[31] Vulnerable populations, including those from low-income or low socio-economic backgrounds and underserved communities, face barriers like limited access to health care facilities, lack of insurance coverage, and financial constraints, hindering their ability to seek timely and appropriate care.[32] Financial toxicity, a term describing the objective financial burden and subjective financial distress, is common among patients with IBD, and is associated with non-adherence to medication and planned health care utilization.[33] In a Canadian study, patients with a lower socioeconomic status had a higher risk of delayed IBD-specific therapy after their diagnosis, as well as a higher risk of long-term non-use of an IBD-specific drug.[34] A subsequent study from Canada showed that individuals of lower socioeconomic status encountered higher rates of hospitalization, prolonged hospital stays, and increased mortality rates, despite comparable access to IBD-specific medications.[35] Studies from the U.S. and the United Kingdom found that people of color were less likely to be prescribed infliximab.[36–38]

Unplanned health care utilization, including emergency department visits and hospitalizations, drives much of the cost in IBD care.[39] American patients insured by Medicaid[40] or without health insurance generate considerable unplanned health care costs.[41] A U.S. study found that 1 in 8 patients with IBD had food insecurity and lacked adequate social support, which was associated negatively with unplanned health care utilization.[42] These data suggest that low-income status conveys an increased risk of not being able to access timely and effective care, to the detriment of long-term health, disease prognosis, and overall cost.

In regions such as South America and Eastern Europe, access to therapies for IBD is more limited,[43–45] which further complicates efforts to achieve cost sustainability. This lack of affordability not only strains health care budgets but also compromises patients' health outcomes, as they may be unable to access the most effective conventional or advanced treatments for their IBD. Variability in health care provision similarly extends to rural areas, whose smaller populations may have limited access to early diagnosis, diagnostic tools, and specialist care.[46]

Practice variability and adherence to guidelines remain key barriers to achieving sustainable care in IBD.[47–49] Suboptimal adherence to international, evidence-based guidelines is an ongoing problem across various aspects of IBD care.[50–52] The absence of standardized guidelines for cost-effective care delivery presents a formidable challenge in achieving cost sustainability.[6] Even when providers adhere to guidelines, patients may defer or skip high-value care due to high out-of-pocket costs. Furthermore, insurance restrictions, such as prior authorizations and fail-first policies, may still limit appropriate adherence to guidelines or access to effective and high-value care, even for patients with adequate insurance coverage.[53,54]

Strategies for Making IBD Care Sustainable

Early implementation of biologic therapies and achievement of deep, endoscopic remission is recommended by guidelines to minimize long-term complications, malignancies, surgeries, and hospitalizations.[55] However, the availability of biologics and infusion centers is often limited outside of high-resource regions, and some studies have shown similar spending without change in hospitalization rates. The U.S. continues to have higher biologic uptake than Canada and Europe, but at substantially greater expense due to ineffective negotiation with pharmaceutical companies. Herein, we will discuss strategies to prevent hospitalization via rigorous medical treatment targets, to streamline price negotiations in non-national payer systems, and to harness preventative care metrics, patient-reported outcomes, and multidisciplinary teams to improve our overall IBD care.

A Focus on Cost-effectiveness in Settings With Limited Resources

Early treat-to-target paradigms lead to durable, steroid-free remission and improved disease outcomes for patients with IBD.[56] However, there are no guidelines as to when biologic medications can be de-escalated or withdrawn while preventing morbidity,

hospitalization, or need for surgery. The IBD Emerging Nations Consortium describes low biologic uptake in Asia (4% in UC, 13% in CD), greater reliance on thiopurines, and substantially lower direct drug-related costs in Asia than in Europe or North America ($1,051–$3,755, compared with $5,938–$10,484 and $8,053–$13,212). This group recommended discontinuing any biologic within 2 years after initiation, presenting findings that only 32% of patients relapsed at 2 years of follow-up (fewer still, if only considering patients in deep remission).[57] Other lower-cost and evidence-based treatments recommended for low-risk patients include dietary therapy, initial surgery for CD, fecal microbiota transplant for UC, and complimentary therapies. Still, these recommendations take aim at high direct drug, procedural, and monitoring costs without maximizing disease control or indirect, patient-reported outcomes; therefore, they are primarily considerations for resource-limited areas.[57]

Promise of Biologics to Reduce Direct Costs

Using a "top-down" clinical paradigm, guidelines suggest starting biologic medications early to induce remission of moderate-to-severe IBD, thereby reducing risk of complications, surgeries, and hospitalizations and improving quality of life.[55,58] A randomized controlled trial demonstrated a clear benefit in steroid-free and surgery-free remission among patients randomized to top-down vs step-up care (79% vs 15%; $P < .0001$).[58] Still, under 20% of private insurance companies in the U.S. permit the use of first-line biological therapy.[59] Studies have been mixed as to whether the cost savings from hospitalizations and surgeries outweigh the exorbitant costs of biologic medications. A systematic review suggested that biologics were cost-effective in CD for a maximum duration of 2 years.[60] A Canadian group showed increased direct costs over the past decade, with anti-TNF therapies alone now representing 70% of total CD costs and 60% of total UC costs.[15] However, a prospective Danish study with 10-year follow-up showed that biologic use to implement early disease control led to lower direct costs at 10 years. Indirect costs (ie, education, workplace achievement, taxes paid, and sick days taken) were high but not higher than the general population, possibly related to the social support from welfare provisions in Denmark.[61] Such clear data are difficult to obtain in the U.S. due to multi-payer systems and obscure pricing incentives used to reduce market competition from biosimilars.

Biosimilars: Promises, Untapped Possibilities, and Legal Thickets

Biosimilars are clinically comparable, nearly identical versions of molecularly complex biologics that can be marketed after originator biologics lose patent exclusivity. Infliximab biosimilars were introduced first in Europe, taking up 13% of the market share at 2 years and 52% by 5 years.[62] Denmark, availing itself of its universal health system, achieved a remarkable 95.1% adalimumab biosimilar uptake within 4 months, cutting costs by 82.8%.[63]

In the U.S., biosimilar entry and uptake have been relatively modest. This difference is explained by the early lack of regulatory environment, prevention of biosimilar entry by originator manufacturers through several legal approaches, and reimbursement dynamics. First, U.S. biosimilar entry was delayed by the lack of a U.S. Food and Drug Administration regulatory framework. The Biologics Price Competition and Innovation Act established a regulatory framework for the approval of biosimilars. However, biosimilar entry was delayed by several approaches employed by manufacturers of originator biologics to extend market exclusivity periods. A good example is that of Humira (adalimumab). After original patent expiry in 2016, the market entry of adalimumab biosimilars was delayed by 7 years via 165 additional patents that granted additional protected years. This practice has been dubbed a "patent thicket" because of the dense obfuscation of hundreds of patents pertaining to the same product. In addition to slowing the approval process for other novel patents, pharmaceutical companies have been appending "terminal disclaimers" to these patents, meaning the follow-on patents expire when the original patent does. Thus, companies aiming to manufacture biosimilars must design around hundreds of complex, frequently litigated patents. Most patent thickening occurs within the year prior to the original patent's expiration. Among 12 biologics nearing biosimilar competition, 271 patents were filed, 48% of which included terminal disclaimers regarding subtle tweaks on mode of treatment and formulation. In 2022, a bipartisan group of senators attempted to eliminate the use of terminal disclaimers[64]; this practice is already illegal in Europe.

After actual market entry, biosimilar market uptake in the U.S. has been hindered by market dynamics related to the reimbursement of products. Although manufacturers of originator small molecule drugs do not compete with generics after loss of exclusivity, manufacturers of originator biologic products offer confidential discounts to payers, out-competing biosimilars. For example, while the list price for infliximab more than doubled in 2007 to 2018, increased confidential discounts negotiated between manufacturers and insurers actually resulted in decreased net prices.[65] Similar trends have been observed for self-administered biologic products.[66]

The financial Incentives associated with these discounting and reimbursement practices differ across payers, which explains the wide variability of biosimilar uptake across payers in the U.S. For instance, the Veterans Health Administration (VHA) has encouraged

biosimilar switching by designating them for preferred use in the national formulary. However, the VHA is a closed system, the only one in the U.S. with a national formulary. Although these VHA efforts have been more effective than non-VHA academic settings, still only 38% of veterans were switched to biosimilar infliximab within 4 years of launch, despite a potential 81% cost savings.[67] This unrealized potential was attributed to poor provider and patient awareness, poor acceptance of interchangeability, and supply chain limitations.[68,69] The Kaiser Permanente system, the largest integrated delivery system in the U.S., has been more successful at biosimilar adoption.[70] Across the remaining market, however, biosimilars have seen modest adoption, as payers often favor originator biologics with higher list prices and higher discounts than biosimilars. This is particularly the case of Medicare, the largest purchaser of drugs in the U.S.[71] The passage of the Inflation Reduction Act in 2022 should yield savings to Medicare, although medications with a biosimilar available may be exempt. The biologic therapy ustekinumab is 1 of 10 selected products for negotiation in the first year of implementation of the program, which will be expanded to provider-administered drugs in 2028. This Act includes 2 additional drug-related provisions that are relevant to U.S. patients covered under Medicare. First, out-of-pocket costs for self-administered products will be limited at $2,000 per year, which will bring financial relief for patients using self-administered biologic therapies; and second, manufacturers will have to pay back to Medicare increases in prices above inflation, which is expected to slow down post-launch price increases.

Using Teams and Technology to Prevent Hospitalizations

Severe disease, high cost of medications, health care-related anxiety, and low resilience all worsen IBD symptoms. The notion of an "IBD Medical Home" is based on primary care models of patient-centered medical homes under the Affordable Care Act (2010). IBD medical homes integrate a team of physicians, psychologists, social workers, dieticians, and dedicated nurses who proactively monitor high-risk patients, aiming to capture flare symptoms and psychosocial stressors before the patient requires emergent care.

This model was deployed by the University of Pittsburgh Medical Center in partnership with a regional private insurer. Implementation of their University of Pittsburgh Medical Center Total Care–IBD program resulted in 47.3% fewer emergency department visits, 35.9% hospitalizations, and $2,500 savings per patient per year.[72] Quality of life and symptom control also improved. Low quality of life and use of opiates or steroids preceding enrollment predicted hospitalization, prompting focus on targets for early intervention in the psychosocial domain.[73] The University of California Los Angeles targeted "value-oriented care," adding work productivity and activity assessments to regular patient-reported clinical inventories collected. Illinois piloted a proprietary patient symptom index called "SONAR" to capture flares prior to their onset.[74] Still, a single-center randomized controlled trial showed no difference in charges per patient between usual care and a patient-oriented intervention arm, which used a care coordinator for proactive monitoring and individualized multidisciplinary care. This intervention improved patient symptom scores, but both arms over the study period had decreased costs, leaving the true cost-effectiveness of such interventions unclear.[75]

Mount Sinai Hospital demonstrated that early access to such multidisciplinary care among patients just diagnosed with IBD reduced steroid courses and improved clinical remission.[76] Multiple centers dedicate inpatient hospital services to the exclusive care of patients with IBD, coordinating with a dedicated nurse who follows proactively after discharge, reducing costs related to longer hospital stays.[77] These interventions can be particularly effective in reinforcing preventative care guidelines (ie, vaccines, tuberculosis screens, hepatitis B checks), although the data are mixed as to whether electronic medical record-based interventions and dedicated care coordinators consistently reduce steroid course prescriptions.[78] Ongoing cycles of innovation and process to improve quality are central to any true IBD Medical Home.

Outside the U.S., a Canadian telemedicine program saved $47,565 in costs while reducing time to specialist establishment.[72] A Dutch pragmatic, multicenter, randomized controlled trial demonstrated the utility of a nurse-driven telemedicine program that drew upon personalized treatment plans, patient-reported outcome inventories, and health questionnaires, to identify early and intervene upon patients at risk for hospitalization of flare, while not overwhelming the need for gastrointestinal physician visits.[79] This program resulted in lower mean annual costs of €612/patient without changing quality-adjusted life-years.[80] Clearly, multidisciplinary care teams leveraging technology and patient-reported outcomes hold great promise to reduce direct and indirect costs, while putting the patient at the forefront.[81]

Conclusions

As the prevalence of IBD continues to increase, so will the financial burden it places on health care systems across the world. Addressing the increasing direct and indirect costs to patients, their families, and society demands a comprehensive strategy, tackling disparities, access barriers, and cost-effectiveness of therapeutics. It will also require policy reforms that improve access to IBD care (Table 1). Achieving these goals requires actions from health care providers, payers, and regulators. Figure 2 summarizes measures that could be

Table 1. Proposed Policy Reforms to Improve Access to IBD Care and Treatment

Reform prior authorization processes	Regulate the prior authorization process, prevent unnecessary delays through the development of policies that limit pharmacy and provider administrative burden and limit the time window where insurers can decline coverage.
Limitation of utilization management tools	Limit the number of unique products onto which insurers can impose utilization management tools within regulated markets.
Ensure access to manufacturer patient assistance programs	Advocate for policies that limit insurers' ability to prevent patients from benefiting from manufacturer patient assistance programs (copayment accumulators).
Address uninsured populations	Call for comprehensive measures to address health care coverage gaps and provide access to affordable health care services and medications, facilitating excellent longitudinal medical care for all patients with IBD, regardless of insurance status, socioeconomic background, comorbid substance use disorder or psychiatric illness, or ethnic, racial, or other minority status.
Enhance transparency in drug pricing	Advocate for policies that promote transparency in drug pricing, including disclosure requirements for manufacturers and insurers.
Introduce value-based reimbursement structures	Foster the deployment of formulary and benefit design structures that are based on value (ie, where cost-sharing and utilization management tools are not guided by drug costs alone, but also by value only but rather by value in a given patient population).
Support eHealth expansion	Advocate for the expansion of eHealth services and reimbursement policies to improve access to care for patients with IBD, particularly those in underserved or rural areas.
Invest in IBD research and education	Call for increased funding for research on IBD prevention, treatment, and management, as well as public education initiatives to raise awareness of IBD and the available resources.

IBD, Inflammatory bowel disease.

implemented by clinicians and to help in reducing costs. By embracing innovative approaches and collaborative efforts across health care systems, we can advance towards a future where personalized, cost-effective care is accessible to all individuals living with IBD, ensuring better outcomes and greater sustainability.

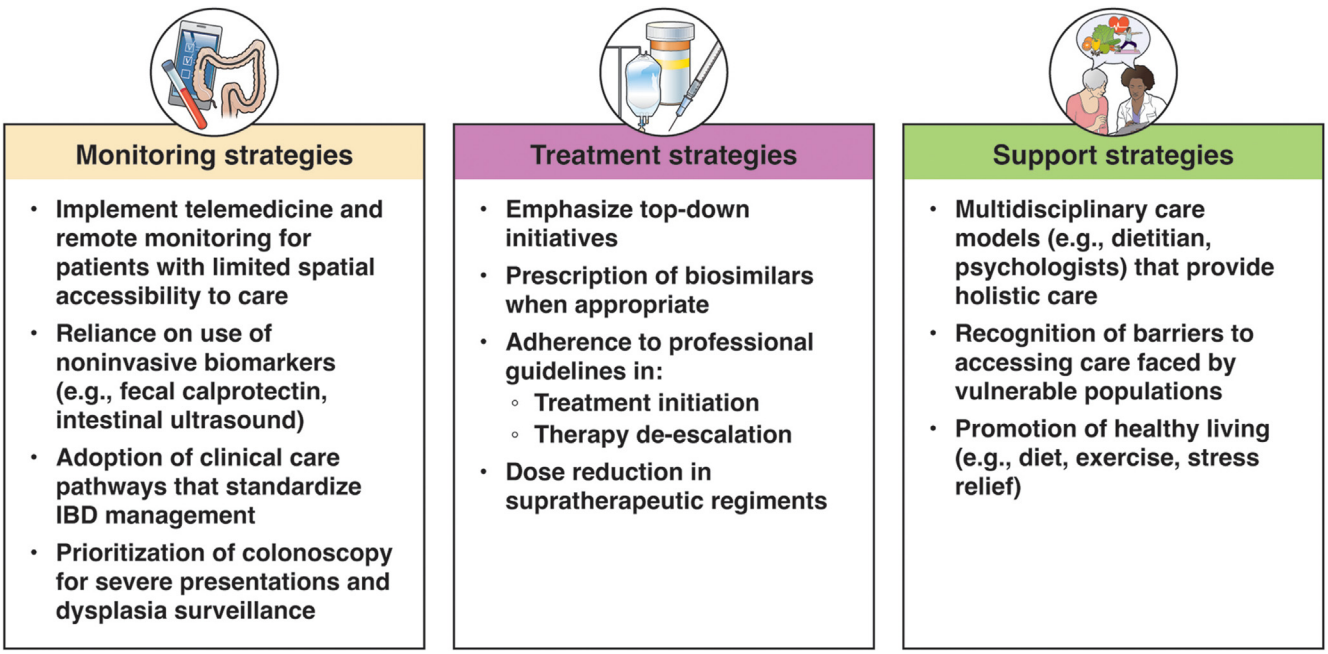

Figure 2. Strategies for cost reduction in the clinical treatment of IBD.

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Conflicts of interest
These authors disclose the following: Johan Burisch reports personal fees from AbbVie; grants and personal fees from Janssen-Cilag; personal fees from Celgene; grants and personal fees from MSD; personal fees from Pfizer; grants and personal fees from Takeda; grants and personal fees from Tillots Pharma; personal fees from Samsung Bioepis; grants and personal fees from Bristol Myers Squibb; grants from Novo Nordisk; personal fees from Pharmacosmos; personal fees from Ferring; and personal fees from Galapagos. Inmaculada Hernandez reports consulting fees from Bristol-Myers Squibb and Pfizer. Jason Ken Hou has received research funding from Redhill Biosciences, Janssen, Abbvie, Celgene, Genentech, Eli Lilly, Lycera, and Pfizer Inc; and has served as a consultant for Eli Lilly. Gilaad G. Kaplan has received honoraria for speaking or consultancy from AbbVie, Amgen, Janssen, Pfizer, and Takeda; has received grants for research from Ferring and for educational activities from AbbVie, Bristol Myers Squibb, Ferring, Fresenius-Kabi, Janssen, Pfizer, Takeda. He shares ownership of a patent (Treatment of Inflammatory Disorders, Autoimmune Disease, and PBC. UTI Limited Partnership, assignee. Patent WO2019046959A1. PCT/CA2018/051098. 7 Sept. 2018). The remaining authors disclose no conflicts.

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Prediction and Prevention of Inflammatory Bowel Disease

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Why do we Need to Discuss Prediction and Prevention?

Although major advances in drug development and therapeutic strategies have been achieved in inflammatory bowel disease (IBD), remission is still far from a universal experience, and there is a persistent treatment gap that exists in IBD.[1] IBD is today a global disease, reaching low-resource communities where care may not be affordable.[2] Once clinical symptoms have occurred, disease processes are irreversible, and there is no cure; furthermore, most patients relapse within a short term if therapeutic de-escalation is attempted.[3] However, it remains possible that there may be a point in the preclinical or early phases of disease that an intervention may reverse or arrest some of the early disease changes, thereby preventing disease from manifesting. These data highlight the need for research into the factors driving IBD development, and to embrace the paradigm shift of prediction and prevention. There is now strong evidence that the clinical onset of IBD is preceded by a preclinical phase, as observed for several other immune-mediated disorders.[4–6] By leveraging samples from unique "pre-disease" cohorts (Supplementary Table 1), researchers have identified biomarkers that can precede the diagnosis of IBD by up to 10 years.[7] Integrated analysis of these markers is underway to understand the pathways that drive IBD development, allowing the development of risk prediction models and the identification of novel therapeutic targets that could be used for prevention trials.[8] Herein, we review the recent insights from studies of the pre-clinical phase of IBD and hypothesize about potential prevention strategies that may be applied in the future.

Learnings from Preclinical Studies

A plethora of biomarkers predictive of future risk of IBD have now been discovered, some of which also shed insight into disease pathogenesis (Table 1). The diverse nature of these biomarkers, as well as the heterogeneity seen in clinical manifestations of IBD, also suggests that several and co-occurring pathways might lead to IBD development.

Genetic Biomarkers

One of the most convincing pieces of evidence illustrating how different mechanisms contribute to IBD is the case of very early onset IBD, whereby host genetics are the main contributor to disease pathogenesis.[18] In general, the role of host genetics in non-very early onset-IBD development is much weaker, although genetics remain one of the earliest biomarkers available to estimate the risk of IBD in a given population. However, genetics alone only explains about 13.6% and 7.5% of the total disease variance of Crohn's disease (CD) and ulcerative colitis (UC), respectively,[19] and is insufficient to accurately identify populations at high-risk for IBD.[20,21]

Environmental Risk Factors

Early life is a critical period for immune maturation and microbiome establishment and thus may represent a critical period for risk modulation.[22] For example, early-life exposure to urban environment, intrauterine exposure to tobacco smoke, infections, and antibiotics have been shown to be associated with increased risk of IBD, whereas breastfeeding and living in a rural environment have been associated with decreased risk.[23,24] Epidemiologic studies in adults have also identified numerous risk factors for IBD, such as Western diet, physical

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Abbreviations used in this paper: AUC, area under the curve; CD, Crohn's disease; FCP, fecal calprotectin; FDR, first-degree relative; GM-CSF, granulocyte macrophage-colony stimulating factor; IBD, inflammatory bowel disease; UC, ulcerative colitis.

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Table 1. Biomarkers Predictive of Future IBD Risk

Omic/marker studied	Repository and type of study	Number of individuals/ samples	Analysis performed	Time before diagnosis -sample obtained, *years*	Main findings
Microbiome[9]	Prospective cohort of first-degree relatives of patients with CD	73 pre-CD / 3410 healthy	16S rRNA sequencing	2.9 years	Microbiome community is associated with risk of CD
Microbiome[10,11]	Prospective cohort of first-degree relatives of patients with CD	Nested cohort 13 pre-UC / 48 healthy	16s rRNA sequencing, shotgun sequencing, enzymology	4.4 years	Protease and elastase activity and *Adlercreutzia* are associated with UC risk
Fecal metabolome[9]	Prospective cohort of first-degree relatives of patients with CD	56 pre-CD / 66 healthy	Ultra-high performance liquid chromatography/tandem accurate mass spectrometry	2.5 years	24 fecal metabolites are associated with CD risk
Gut barrier[12]	Prospective cohort of first-degree relatives of patients with CD	50 pre-CD / 1370 healthy	Urinary fractional excretion of LMR	2.95 years	An abnormal LMR (>0.03) was associated with a diagnosis of CD
Proteomics[13]	Prospective cohort of first-degree relatives of patients with CD	Nested cohort 71 pre-CD / healthy 284	446 serum proteins from 5 Olink panels inflammation, cardiometabolic, cardiovascular, cardiovascular III, and immune-response	2.0 years	25 serum proteins significantly associated with future development of CD
Proteomics[14,15]	Retrospective study using serum samples from the DoD serum repository	Nested case-control study, 200 CD and 200 controls, 3-4 serum samples per individual	1129 proteins (SomaLogic) involved in sim	Multiple time points, furthest at 6 years before diagnosis	51 protein biomarkers predictive of CD at 6 years before diagnosis (an AUC of 0.76 at 5 years to 0.88 at 1 year before diagnosis) Pathways related to glycosylation, complement, lysosome, and innate immunity differently expressed in the serum years before diagnosis Specific proteins associated with CD complications at diagnosis
Proteomics[16]	Nested case-control study (Northern Sweden Health and Disease Study register cohort)	72 individuals who developed UC vs 140 controls	Proseek Multiplex Inflammation I Probe kit 96x96 (Olink Bioscience)	4.8 years	Six proteins (MMP10, CXCL9, CCL11, SLAMF1, CXCL11, and MCP-1) were up-regulated ($P < .05$) in preclinical UC compared with controls based on both univariate and multivariable models.

Table 1. Continued

Omic/marker studied	Repository and type of study	Number of individuals/ samples	Analysis performed	Time before diagnosis -sample obtained, *years*	Main findings
Antibody response[17]	Prospective cohort of first-degree relatives of patients with CD	Nested cohort 77 pre-CD / healthy 307	anti-Saccharomyces cerevisiae antibodies immunoglobulin A/ immunoglobulin G, anti-OmpC, anti-A4-Fla2, anti-FlaX, anti-CBir1	2.2 years	Increased anti-microbial antibody responses are associated with risk of future development of CD, independent of biomarkers of abnormal gut barrier function, subclinical inflammation, and CD-related genetic risks
Antibody response[14]	Retrospective study using serum samples from the DoD serum repository	Nested case-control study, 200 CD and 200 controls, 3-4 serum samples per individual	anti-Saccharomyces cerevisiae antibodies immunoglobulin A/ immunoglobulin G, anti-OmpC, anti-A4-Fla2, anti-FlaX, anti-CBir1	6 years	Predictive performance from 0.69 at 5 years and 0.76 at 1 year before diagnosis
Auto-antibodies	DoD serum repository	Nested cohort, 82 pre-UC, 82 HC	ELISA against anti-integrin $\alpha v\beta 6$	10 years	Predictive performance from 0.79 at -10 years to 0.89 at -2 years before diagnosis
Auto-antibodies	Prospective cohort of first-degree relatives of patients with CD	Nested cohort 12 pre-UC / healthy 49	ELISA against anti-integrin $\alpha v\beta 6$	4.2 years	Anti-integrin $\alpha v\beta 6$ is associated with UC onset

AUC, Area under the curve; CD, Crohn's disease; ELISA, enzyme linked immunosorbent assay; IBD, inflammatory bowel disease; LMR, lactulose to mannitol ratio; UC, ulcerative colitis.

activity patterns, exposure to pollutants, and personal smoking habits, suggesting that environmental and dietary exposures may continue to modify risk of IBD into adulthood.[12,25]

The Gut Microbiome and Intestinal Permeability

Dysregulation of the gut barrier function, altered microbiome composition and function, and antimicrobial antibody reactivity are detectable long before disease is diagnosed.[14,17,26] It is tempting to speculate that increased gut permeability may promote translocation of microbes or microbial products,[27] leading to activation of host immune responses and triggering local gut inflammation. Recently, alterations in specific gut microbial communities were shown to be associated with risk of CD onset in the CCC-GEM cohort. Individuals with a high microbiome risk score, characterized by increased *Rumnicoccus torques* and *Blautia* and decreased *Faecalibaterium*, were 2.24-fold more likely to develop CD. This increased risk for CD remained significant even in individuals with low fecal calprotectin (FCP), a marker of intestinal inflammation.[9] Additionally, relative abundance of *Adlercreutzia* has been associated with an increased risk of UC.[10] Although these studies were conducted in first-degree relatives (FDRs) of those with CD, and thus cannot be directly extrapolated to the general population, gut microbial patterns of healthy FDRs have been shown to be similar to those of healthy individuals,[28,29] suggesting this may also have potential as a biomarker in the general population. However, it remains unknown whether the microbiome or gut permeability independently or jointly promote disease onset, as the gut microbiome is directly associated with gut permeability.[30] Finally, metabolomic signatures also suggest that steroid hormone biosynthesis and microbial dysregulation can be detected many years before disease onset.[9,31]

Dysregulated Immune Responses Predate IBD Onset

Serum proteomic assessments in pre-disease cohorts indicated that several proteins related to a dysregulated immunity are associated with future CD. Moreover, 2 studies using different proteomic platforms found that 9 of 10 proteins have similar direction of effect in 2 independent pre-disease cohorts, suggesting that a proteomic signature of preclinical CD could be used to screen at-risk individuals.[13,14] In addition, increased antibodies to granulocyte macrophage-colony stimulating factor (GM-CSF), a cytokine involved in the promotion of antibacterial and immunomodulatory functions, is detected many years before CD onset.[32] GM-CSF is also a predictor of complicated CD at diagnosis. Increased C-reactive protein and FCP are also both associated with increased risk of future CD, although the individual predictive values of these for disease onset is poor. Data from the CCC-GEM project showed that 93% (515/555) of participants with elevated FCP (>120 μg/g) remained asymptomatic during a mean follow-up duration of 6 years and up to a maximum of 11.4 years of follow-up.[9] This suggests that a pre-clinical phase with elevated FCP may exist years or even decades before symptomatic disease begins.

At some point, endoscopic and histological lesions may develop before clinical symptoms. In a prospective study of 480 healthy FDRs, those in the highest and lowest quartiles of a calculated risk score (including polygenic risk score and smoking) underwent video capsule endoscopy. Overall, 21% (n = 22) had a Lewis score $\geq$135, indicating at least mild inflammation, and 11 from the high-risk group had a Lewis score $\geq$790 (moderate to severe inflammation). One individual was diagnosed with CD during the 3-year follow-up.[33] However, nearly 80% of subjects had no evidence of inflammation on video capsule endoscopy. Additional evidence that minor endoscopic lesions develop prior to symptoms comes from colorectal cancer screening programs, where incidental diagnoses of IBD have been described in 0.35% of patients.[34] Altogether, these support the hypothesis that endoscopic lesions may precede symptom onset, but that the majority of those with elevated biomarkers do not have evidence of mucosal damage.[34,35] This highlights that the long and variable pre-disease phase may provide ample opportunities to meaningfully slow or prevent disease.

It is worth highlighting that, so far, it has been difficult to identify biomarkers associated with pre-clinical UC. Nonetheless, using serum samples from the PREDICTS Cohort,[36] anti-Integrin $\alpha v\beta 6$ autoantibodies predicted UC development with an area under the curve (AUC) of 0.8 up to 10 years before diagnosis.[11] Using serum samples from the Northern Sweden Health and Disease Study register dataset, 6 proteins were found to be differentially regulated between preclinical ulcerative colitis and controls, albeit with moderate AUC for predicting diagnosis (AUC, 0.71; 95% confidence interval, 0.63-0.78).[16] It may be that UC (and even CD) preclinical stages should be explored in other compartments besides the serum. Alternatively, future pre-disease cohorts may require a larger number of pre-UC cases or dedicated recruitment of FDRs of UC to better query for specific pre-UC biomarkers.

Who Could Benefit from Screening and Prevention?

Population-based screening for pre-clinical biomarkers of disease is likely neither feasible nor cost-effective. Thus, risk stratification methods are needed to identify high-risk populations. FDRs of those with IBD, particularly CD, have a roughly 3- to 10-fold increased risk of IBD and a lifetime risk of 2% to 7%.[37] This risk

further increases with number of affected FDRs, younger age of onset of the affected FDR, and Ashkenazi Jewish ancestry.[37–39] Twin studies have shown concordance rates as high as 55% for CD and 19% for UC in monozygotic twin pairs.[40] Those with other immune-mediated inflammatory diseases also have a 2- to 3-fold increased risk for CD, specifically, particularly with diagnoses such as ankylosing spondylitis, psoriasis, rosacea, atopic dermatitis, or multiple immune-mediated inflammatory diseases.[41,42] Thus, clinical parameters such as personal and family medical history are a first step to easily identify those who would benefit most from further risk assessment and prevention programs for IBD.

Once high-risk individuals have been identified, subsequent testing to further risk stratify may include assessment for pre-clinical serum biomarkers such as anti-Saccharomyces cerevisiae antibodies, anti-GM-CSF antibodies, $\alpha v\beta 6$ auto-antibodies, or proteomic biomarkers; assessment of stool biomarkers such as microbiome analyses or metabolomics; assessment of intestinal permeability; as well as evaluating for markers of subclinical inflammation using FCP. These may then be used to define personalized prediction and even personalized mechanisms of disease that inform selection of preventive interventions (Figure 1).

When to Intervene?

Although a clinical diagnosis of IBD requires the presence of clinical symptoms/signs and compatible endo-pathological findings, data has shown that disease processes actually begin earlier.[11] The exact point in time when preclinical disease or risk starts remains unclear. In other disease areas, cohorts with prolonged longitudinal follow-up have shown that biomarkers may be detectable as early as 20 years before disease onset.[43] In IBD, it is conceivable that modulation of risk could begin as early as the period of early life. This is supported by experimental and epidemiological data.[23] At this time, it should be emphasized that the exact chronological order of events leading to IBD remains unknown. Few longitudinal studies in high-risk populations have been done. The Department of Defense Serum Repository (DoDSR) is one such cohort of pre-disease individuals with access to serological events that preceded IBD onset up to 10 years before diagnosis.[14] Using this powerful study design, antimicrobial antibodies were shown to be detected and stable long before IBD onset. Thus, these signatures might be one of the earliest markers of the disease.

The ECCO scientific workshop has proposed a conceptual model, with different stages for the preclinical period, based on the available evidence. It is conceivable that in those who are at-risk (Stage 1: at risk), interactions between microbial, host genetic, and environmental factors trigger initial changes such as altered intestinal permeability and/or dysregulated immune responses (Stage 2: disease initiation), which eventually contribute to increased mucosal immune activation, elevated inflammatory serum markers, and mucosal injury (Stage 3: disease expansion), and ultimately clinical symptoms (Stage 4: diagnosis).[44] It is plausible that the probability and the time until disease development will change as immunological changes accumulate and as the inflammatory cascade expands. It is unclear at which point in time disease processes become irreversible, but based on different probabilities of disease development, we foresee that different interventions, and risk/benefit assessment from those interventions, could be tailored at different preclinical stages.

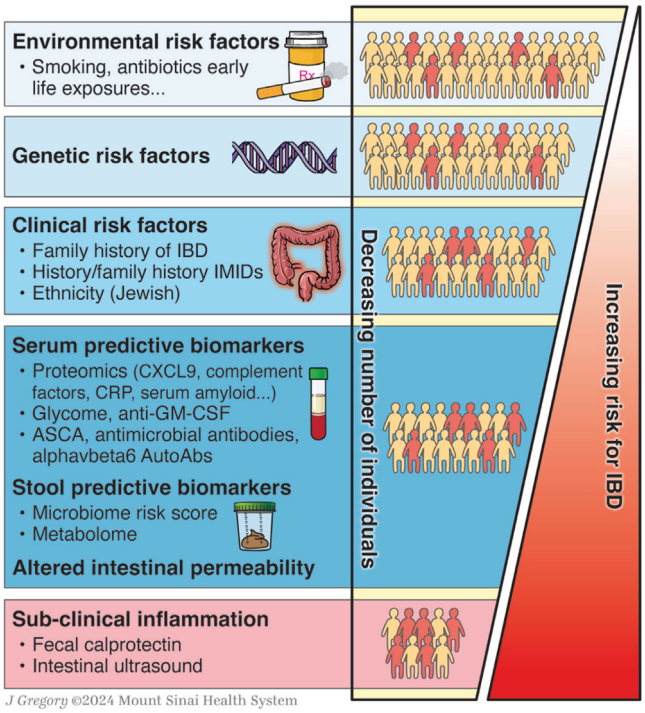

Figure 1. Risk-stratification of individuals at-risk may allow selection of those with the highest risk for disease development, who may benefit from tailored interventions.

What Could be the Intervention(s)?

Developing a preventive approach will first require adequate risk-stratification, potentially using disease risk scores, to ensure that potential benefits of therapy outweigh the risks, and to tailor therapies to specific pathways that drive individual disease development. Because genetic risk is fixed, potential interventions for IBD prevention must target factors beyond the genetic level such as epigenetics, gut microbial profile, gut barrier integrity, host-immune responses, or environmental influences.

Modulating Early Life Exposures

The first years of life, extending from the intrauterine life to early childhood, represent a critical period when

immune development/maturation and microbiome establishment take place. Increasing epidemiological and experimental evidence suggest that exposures during this period could have an impact on future risk for IBD.[22,23,45] Children born to mothers with IBD have altered microbiome and increased FCP as compared with children born to healthy mothers.[46] The MELODY study aims to understand if dietary intervention in pregnant mothers with CD can impact maternal and neonatal microbiome composition and in turn, immune system development.[47] Although protective early life factors such as promoting breastfeeding, childhood pet exposure, and avoiding unnecessary exposure to antibiotics may be of particular interest to parents with IBD who are concerned about IBD risk in offspring, additional research is needed to determine the impact of early life interventions.

Lifestyle and Dietary Intervention

Factors that are readily modifiable, such as diet and lifestyle interventions, are attractive targets for IBD prevention because of their low risk, low cost, and ease of clinical assessment.[48] Numerous dietary and lifestyle risk factors have been identified for IBD, including cigarette smoking, low physical activity, and Westernized dietary patterns, including processed food or altered fiber constituents.[25,49] Pre-disease cohorts have shown associations between Western diets and increased FCP, as well as altered microbiome composition.[50]

Human studies have begun to explore dietary interventions in treating established IBD, such as enteral nutrition and diets low in processed foods or emulsifiers (such as the Mediterranean diet and "anti-inflammatory" diets). These may guide dietary interventions for disease prevention, as well. The Mediterranean diet, widely accepted to reflect a healthy dietary pattern, has been linked with lower risk for CD.[51] In a prospective study of 6 United States and European cohorts, adherence to a healthy diet, physical activity, and smoking avoidance could have prevented 61% of CD cases and 42% of UC cases in the population,[52] assuming a causal relationship. Further, healthy diet, physical activity, and smoking avoidance also have established benefits outside of IBD prevention including lowering cardiovascular disease and cancer risk.[53] Thus, although the benefits of such recommendations for IBD prevention are unlikely to be verified in a randomized controlled trial setting (given the large group size requirements, prolonged time between intervention and clinical benefit, and issues with cost and follow-up), recommendations for smoking cessation, regular physical activity, and adhering to a Mediterranean diet can be broadly recommended to those at risk for IBD with little risk and potential benefit across multiple domains of health. However, diet and lifestyle interventions can be challenging to implement, and may be insufficient to prevent IBD development in those whose risk is driven primarily by other pathways.

Microbiome-targeted Strategies

Because the microbiome likely plays a central role in disease pathogenesis, it may be a target for therapeutic intervention.[9] This might be accomplished through dietary manipulation of the microbiome or with microbially targeted treatments. Fecal microbiota transplant for the treatment of established IBD has had inconsistent success. However, active inflammation can in turn affect gut microbiome composition; thus, it remains to be determined if microbial manipulation such as fecal microbiota transplant prior to overt clinical IBD can impact preclinical disease course. More precise microbiome interventions may benefit specific subpopulations defined by genetic or serologic markers. For example, polymorphisms in the bacterial peptidoglycan sensing NOD2 gene have been associated with increased abundance of *Erysipelotrichaceae* in unaffected FDRs, but with relatively little influence on overall gut microbiota composition.[54] In patients with established CD, those who produced the anti-microbial anti-OmpC antibodies had higher remission rates to budesonide treatment when also receiving ciprofloxacin and metronidazole.[55] Further, metronidazole has been shown to help prevent postoperative CD recurrence.[56] Thus, it is tempting to consider that targeted antibiotics may play a role in restoring gut microbial balance in certain at-risk subpopulations. However, in general, antibiotics contribute to decreased bacterial diversity and increased Proteobacteria, which confer risk for IBD, and contribute to pathogenic bacterial resistance. Thus, alternatives strategies that may be used to modulate the microbiome in a targeted fashion include bacteriophages, bacteriocins, probiotics, or monoclonal antibody therapies.[57]

Barrier Dysfunction

It would be reasonable to consider that strengthening the gut barrier function could help prevent disease. Manipulating microbe-host interactions in subjects with altered barrier function could be one possible approach.[30] Probiotics and prebiotics, particularly through the development of short-chain fatty acids, may also help promote intestinal barrier integrity.[27,58] In addition, there are small molecules being developed to alter barrier function.[59]

Altered Glycosylation and Anti-GM-CSF

Over 20 genes involved in glycan biosynthesis have been linked with IBD risk.[60] Further, glycosylation pathways have been highlighted as some of the key pathways preceding disease onset.[61] In mouse models of colitis, supplementation with synthetic glycans, which are fermented by gut bacteria, reduced weight loss, improved clinical activity scores, and shifted bacterial taxa toward butyrate-producing organisms known to be deficient in IBD.[62] Anti-GM-CSF autoantibodies, which

recognize altered glycosylation of GM-CSF and emerge years prior to complicated CD onset, are associated with pro-inflammatory group 1 innate lymphoid cells.[32] Importantly, stripped GM-CSF lacking glycan structures facilitates escape from anti-GM-CSF recognition, suggesting that de-glycosylated GM-CSF supplementation can restore immune homeostasis in those with neutralizing anti-GM-CSF autoantibodies in the pre-clinical phase.

Targeting Immune Mechanisms of Disease

The earliest events leading to disease need to be defined to prevent disease. The consideration of using any biologic therapy to treat healthy individuals with biomarkers of disease risk will require careful consideration of the balance of the effectiveness of the intervention and potential side effects, as well as cost. Nonetheless, this is already being assessed in other immune-mediated diseases. As an example, abatacept, a soluble CTLA-4 analogue preventing T cell activation, resulted in some delay of development of rheumatoid arthritis.[63,64] On the other hand, 1-year treatment with abatacept in individuals with pre-type 1 diabetes mellitus did not significantly delay progression to glucose intolerance.[65] Lastly, a phase II clinical trial showed that the anti-CD3 antibody, teplizumab, led to a delayed the onset of diabetes in relatives at risk for type 1 diabetes mellitus up to 6 months after treatment.[5] These studies suggest that if specific immune targets can be defined, it may be possible to prevent, attenuate, or delay IBD.[66] Because antibodies to cytokines and microbial-derived antigens such as GM-CSF, flagellin, and anti-Saccharomyces cerevisiae antibody and the integrin $\alpha v\beta 7$are elevated in pre-disease cohorts of CD and UC, it is reasonable to propose that immune targets will need to be considered as a means of prevention in IBD. For example, mouse studies showed that a vaccine using flagellin antigen can alter mouse colitis.[67] One can imagine vaccine strategies aimed at re-establishing tolerance to these antigens or as a means of altering specific gut microbes as a way of preventing disease. Another approach to consider is immune-targeted approaches using regulatory T cells. Small human studies showed an effect of in vitro generated regulatory T cells in CD.[68] There is a lot of interest in development of novel CAR-T cell therapy in which the chimeric antibody is directed to a marker of gut trafficking adhesion molecules or other markers or activated T cells.

Whether medications currently used for IBD, such as 5-aminosalcylates, immunomodulators, biologics, or small molecules may be viable interventions to delay or prevent onset of IBD in the preclinical disease phase remains to be determined.

Implementing Prediction and Prevention: Challenges and Prospects

Although individual biomarkers can help explain biological events that might contribute to the triggering of IBD, they only have moderate to low predictive values when assessed alone. Therefore, any predictive tool should combine different domains and omics, allowing interactive predictive models. It remains to be addressed how strong a predictive assessment should be to target specific high-risk populations when considering possible interventions to prevent disease. Most statistical methods proposed to analyze the high-dimensionality of omics-type data predominately rely on linear models and emphasize associations. A major limitation of such predictive models is that they hypothesize that the predictors and disease outcomes are linear. However, this is not necessarily the case, as illustrated in the CCC-GEM project, where FCP association with risk of CD is not a linear effect.[9] In addition, linear models usually assume independence of the variable assessed, but biomarkers of IBD can be tightly correlated with each other and can involve pleiotropic biological pathways leading to disease.

Several potential barriers exist to implementing screening and prevention programs. First, validated prediction algorithms are needed to identify those at highest risk for developing disease. A critical step for disease prediction is the external verification of predictive biomarkers. Further expanding the sample size and testing in different cohorts (retrospectively or prospectively) will be required to assess feasibility and accuracy at a larger scale. Some of these efforts are underway.[8] Validating a set of predictive biomarkers will hopefully pave the way for prevention trials. Further, the risk or probability of developing disease may change over time, and therefore, it is fundamental that an estimate of time to develop disease is also obtained from biomarker research. Although some biomarkers may be stable over time, others may increase towards the time of diagnosis. Additional research is also needed to better define biological pathways for IBD development that can then be linked to personalized, targeted interventions. No less important is the need to understand the preferences and acceptability of various screening and prevention methods in high-risk populations, such as unaffected FDRs. For example, specific concerns regarding fear of developing IBD or misconceptions regarding IBD diagnosis may prevent high-risk individuals from seeking screening and care. However, preliminary studies have shown that FDRs have high interest in participating in preventive research, such as personal risk assessment and lifestyle or medication interventions for IBD.[69] High-risk clinics, where individuals at risk could come to receive testing, advice, and monitoring, may be one method to both screen and educate high-risk populations on IBD risk and dispel common myths about IBD. Health care access also needs to be considered to ensure equitable screening.

Emerging data regarding serologic and stool-based biomarkers will improve the ability to predict risk of IBD. However, the time to disease development in "at-risk" individuals is variable. Therefore, any study

attempting to measure change in risk development will require large, longitudinal cohorts. The biomarker data currently available suggests that interventions related to diet, microbiome composition and function, barrier dysfunction, and altered immune mechanisms may be primary targets. In addition to defining the appropriate target for such interventions, it will be essential to define the outcome of such trial(s). Given that some biomarkers have been identified many years preceding diagnosis, it may be unrealistic to follow individuals at risk until they develop disease, and therefore an intermediate biomarker that may reflect subclinical inflammation is needed.

Conclusion

In spite of the challenges in developing this new arena of disease prediction and prevention in IBD, it is clear that major advances in understanding the pre-disease stages, the nature of risk, and the nature of possible triggers of disease are paving the way for the development of a new era where disease intervention and disease modification will be a real possibility.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.05.047.

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Conflicts of interest
The authors disclose no conflicts.

Supplementary Table 1. Characteristics of Established Pre-IBD Cohorts

	Study design	Advantages	Limitations
CCC-GEM project	Prospective follow-up of first degree relative of patients with CD	Variety of samples collected, multicentered	Samples collected at recruitment
DoD	Retrospective military personnel screened for HIV	Longitudinal sampling collected before onset.	Majority of participants are male, physically fit. Samples are limited to serum. Diagnostics based on ICU codes. Limited generalizability to the general population.
Nurses' Health Study (NHS), NHSII, and Health Professionals Follow-Up Study (HPFS)	Prospective follow-up of female nurses and male health professionals	Large sample size, long follow-up time	Majority of participants are female, white, and older. Limited generalizability to the general population.
Northern Sweden Health and Disease Study register cohort	Population-based study prospective blood samples and related survey data can be linked to national registries for health outcomes	Large sample size.	Samples are limited to blood and questionnaires. Limited generalizability to other populations.
Danish repository	Nationwide, population-based study using data from continuously updated national health registers in Denmark	Large sample size	Diagnostics based on ICD code, limited biosample collected. Limited generalizability to other populations.
EPIC	Prospective multi-center cohort study of men and women in 10 Western European countries	Large sample size	Limited collection of biosample
Baby teeth cohort	Collection of deciduous teeth from individuals who developed IBD later in life	Assessment of pre- and postnatal period and risk of IBD	Difficulty to replicate findings due to uniqueness of sample type
The MECONIUM study	Prospective follow-up of pregnant women with and without IBD and their newborn babies	Assessment disease transmission in utero and early life of IBD risk	Limited follow-up time and limited number of new onset cases.
The MoMmy-CD study	Prospective follow-up of newborn babies from pregnant women with and without IBD	Assessment disease transmission in utero and early life of IBD risk	Limited number of new onset cases.

Note: This is not an exhaustive list, and we acknowledge there are other cohorts with data yet to be published.
IBD, Inflammatory bowel disease.

Diet and Microbiome-Directed Therapy 2.0 for IBD

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Inflammatory bowel disease (IBD) comprises chronic and relapsing disorders of the gastrointestinal tract, characterized by dysregulated immune responses to the gut microbiome. The gut microbiome and diet are key environmental factors that influence the onset and progression of IBD and can be leveraged for treatment. In this review, we summarize the current evidence on the role of the gut microbiome and diet in IBD pathogenesis, and the potential of microbiome-directed therapies and dietary interventions to improve IBD outcomes. We discuss available data and the advantages and drawbacks of the different approaches to manipulate the gut microbiome, such as fecal microbiota transplantation, next-generation and conventional probiotics, and postbiotics. We also review the use of diet as a therapeutic tool in IBD, including the effects in induction and maintenance, special diets, and exclusive enteral nutrition. Finally, we highlight the challenges and opportunities for the translation of diet and microbiome interventions into clinical practice, such as the need for personalization, manufacturing and regulatory hurdles, and the specificity to take into account for clinical trial design.

Keywords: Crohn's; Diet; Nutrition; Microbiome; Probiotic.

Inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD) and ulcerative colitis (UC), affect millions of individuals globally. They are chronic, progressive diseases that arise due to a dysregulated immune response to a dysbiotic gut microbiome in genetically susceptible individuals.[1] While the initial phase of investigation of the biology of these diseases focused on genetic variants, we have learned that both the external environment including diet[2] as well as the internal microenvironment in the form of the gut microbiome[3] play a critical role in these disease. While still in early phases, interventional studies modulating diet or targeting the microbiome have shown promise and are likely to be an important part of our armamentarium in managing IBD. In this review, we examine the evidence behind the role of diet and the microbiome in the development and progression of IBD. We define some of the gaps in the existing literature and suggest solutions toward achieving a goal of personalized diet- and microbiome-based approaches to treat or prevent IBD.

The Microbiome

Microbiome Alterations and Role in IBD Pathogenesis

The gut microbiome represents the complex ecosystem of microorganisms colonizing the human gut. It plays a major role in human physiology and is under the influence of both host and environmental factors, including diet. Until recently, it was not possible to resolve whether the gut microbiome and its alterations were a true actor in the inflammatory process or an inactive witness of the disease. Although some alterations in the gut microbiota observed in IBD are likely to be secondary events related to intestinal inflammation, there are now sufficient data to affirm that microbiota alterations, whether as primary or secondary events, play an active role in the pathogenesis of the disease. Numerous IBD susceptibility genes are involved in innate and adaptive immune responses to microbes,[4] the luminal content is necessary to induce colitis in mice models and postoperative recurrence in CD,[5] and antibiotics have some efficacy in specific clinical settings.[6] However, some decisive arguments have emerged in recent years, including the fact that (1) alterations in the

Abbreviations used in this paper: **AID, anti-inflammatory diet; CD, Crohn's disease; CDED, Crohn's disease exclusion diet; CDI, *Clostridiodes difficile* infection; CI, confidence interval; EDIP, empiric inflammatory dietary potential; EEN, exclusive enteral nutrition; FMT, fecal microbiota transplantation; FODMAP, Fermentable oligosaccharides, disaccharides, monosaccharides and polyols; FOS, fructo-oligosaccharides; HR, hazard ratio; IBD, inflammatory bowel disease; MDP, Mediterranean diet pattern; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; SCD, specific carbohydrate diet; SCFA, short-chain fatty acid; UC, ulcerative colitis; UPF, ultraprocessed food.**

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gut microbiome precede the onset of CD by several years,[7] (2) the fecal microbiome from IBD patients shows proinflammatory effects when transferred into germ-free mice,[8] and (3) therapeutic modification of gut microbiome, including through fecal microbiota transplantation (FMT), has an impact on disease severity in mouse colitis models and, more importantly, in humans.[9]

A detailed description of the alterations in the gut microbiome associated with IBD is available elsewhere,[10] but we report here the most important ones (Figure 1). A decrease in bacterial diversity associated with greater instability over time has been observed in both UC and CD. An increased abundance of members from the Enterobacteriaceae family that have demonstrated proinflammatory properties in colitis models in mice is observed in IBD.[10] An increased abundance of sulfate-reducing bacteria has been described in UC, and the sulfide that they produce may be toxic for epithelial cells.[11] Conversely, a decline in the relative abundance of members of the Firmicutes phylum, including some anti-inflammatory species such as *Faecalibacterium prausnitzii*, is usually observed.[12] Interestingly, ileal CD is associated with specific microbiome alterations, including an increase in potentially proinflammatory bacteria, such as adherent-invasive *Escherichia coli* and *Ruminococcus gnavus*.[13,14] In addition to the bacterial compartment, alterations in fungi, protists, archaea, and viruses have also been described in IBD. The abundance of *Candida albicans* is increased in IBD and exhibits proinflammatory effects, while another fungus, *Debaryomyces hansenii*, impairs intestinal healing.[15] On the other hand, the abundance of *Saccharomyces cerevisiae*, which may have anti-inflammatory effects, is decreased in IBD.[16] It is important to note that the vast majority of available data on the IBD-associated microbiome come from fecal analysis. This is a major limitation in this field, as feces do not reflect the other compartments of the gastrointestinal system, such as the colonic mucosa or the ileum, that may or may not be altered as well.

Besides alterations in composition, the gut microbiome in IBD is characterized by major metabolic shifts.[17] Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are produced by gut microbiome members from the metabolism of fibers as well as by other dietary components such as resistant starches and polyphenols and exhibit a myriad of beneficial effects on host physiology and particularly on intestinal epithelial and immune cells. Butyrate is notably the primary substrate of colonic epithelial cell energy metabolism. A decreased abundance of butyrate-producing bacteria, such as *F prausnitzii* or *Roseburia intestinalis*, are observed in IBD.[17] The transformation

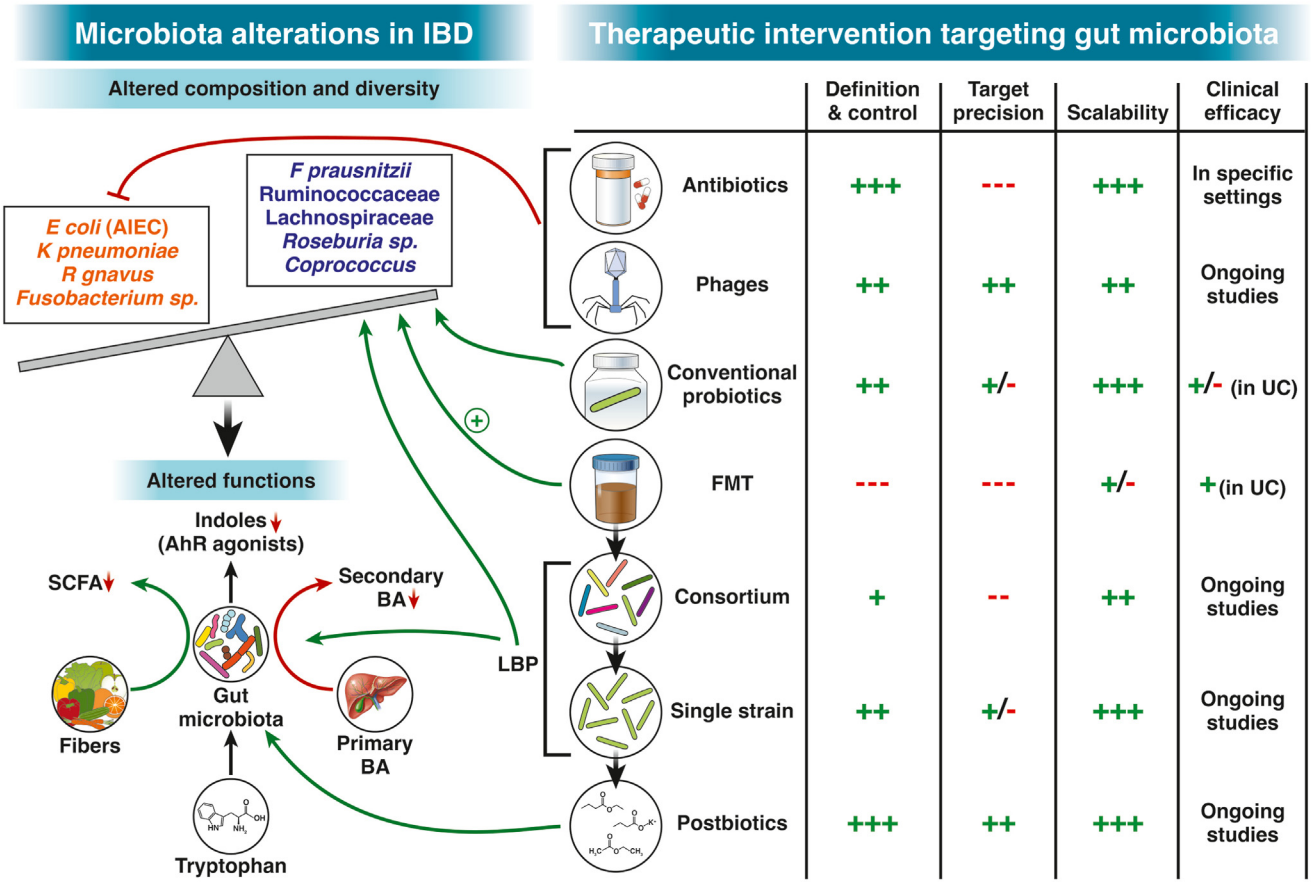

Figure 1. Gut microbiota alterations in IBDs and associated therapeutic interventions. AhR, aryl hydrocarbon receptor; AIEC, adherent-invasive *Escherichia coli*; BA, bile acid; LBP, live biotherapeutic product.

and deconjugation of primary conjugated bile acids produced in the liver by gut microbes into secondary unconjugated is altered in IBD.[18] Finally, the transformation of tryptophan, an essential amino acid, into indole and indole derivatives is a crucial function of the gut microbiome that is altered in IBD. Indeed, several of these tryptophan metabolites are agonists of the aryl hydrocarbon receptor and promote intestinal homeostasis, healing, and immunoregulatory phenotype.[19]

Microbiome Interventions: Prebiotics and Probiotics

Given the central role of the microbiome in IBD, altering the microbiome to modify IBD outcomes is a therapeutic area of interest.

Prebiotics are substrate that are selectively utilized by host microorganisms conferring a health benefit. The most common include fructo-oligosaccharides (FOS), galacto-oligosaccharides, and inulin. There have been several notable findings in animal models of IBD.[20,21] Oligosaccharides increase production of some of the SCFAs, either directly or through cross-feeding, which are known to exhibit anti-inflammatory properties in the gut.[22] Daily administration of FOS and inulin were shown to decrease mucosal proinflammatory cytokines in dextran sulfate sodium models. Human data, however, have been mixed. Several small human trials have had notable findings. Lindsay et al[23] assessed 10 patients with ileocolonic CD that were dosed with 15 g of FOS for a 3-week period. In this study, a decrease in Harvey-Bradshaw index and an increase in fecal bifidobacteria was appreciated. Another trial in both CD and UC randomized participants to microencapsulated sodium butyrate or placebo for 2 months.[24] In both CD and UC patients, treatment was associated with an increase in SCFA-producing bacteria. However, a study in 103 patients showed that inulin/oligofructose did not impact disease activity in CD,[25] and other smaller studies have not shown conclusive evidence of benefit in UC.[26] There has been a double-blind, placebo-controlled trial of FOS in patients with active CD.[25] The primary outcome assessed was clinical response at week 4; the study found no difference in clinical response between the FOS and placebo groups (22% vs 39%) and no differences in fecal *Bifidobacteria* or *F prausnitzii* abundance.

When administered in adequate amounts, probiotics, which are defined as live microorganisms, confer a health benefit to the host. They are generally intended for a healthy population and are regulated as dietary supplements. Probiotics have been assessed as possible therapeutic agents in IBD, particularly in UC. Many trials have focused on induction of remission of UC with various probiotics and results have been mixed. Positive associations have been seen with bifidobacterium. A 2017 meta-analysis identified no significant effect of probiotics overall, but studies of the probiotic VSL#3 showed efficacy in inducing remission compared with placebo (rate ratio, 0.74; 95% confidence interval [CI], 0.63–0.87).[27] A 2021 meta-analysis identified 20 randomized controlled trials (RCTs) of probiotics and 5 RCTs of synbiotics for UC.[28] In this meta-analysis, a statistically significant reduction in UC disease activity index was found for the effects of probiotics, prebiotics, and synbiotics combined (standardized mean difference, 1.00; 95% CI, 0.27–1.73) with significant heterogeneity between studies. There was no significant effect of probiotics alone on UC activity, though 3 RCTs of 2- to 3-strain probiotic blends (*Lactobacillus*, *Bifidobacterium* strains) did show benefit for reducing UC activity. Other strains such as *E. coli* Nissle 1917 and *Lactobacillus* did not show improved outcomes when compared with mesalamine.[29] Tolerance, however, may also be an issue with probiotics in the population, as they can lead to increased gas and bloating as well.

Fewer studies have assessed the efficacy of probiotics for the induction of remission in CD, and most are very small and underpowered. Schultz et al[30] performed a double-blind RCT to investigate oral *Lactobacillus* GG compared with placebo for the induction of remission in CD. In this study, only 5 of 11 patients completed the study, with no significant differences appreciated between groups.

Pouchitis is also an area within IBD in which the utility of probiotics has been explored. According to the American Gastroenterological Association Pouchitis guidelines, there is no recommendation for the use of probiotics for the primary prevention of pouchitis given the lack of data. In patients with recurrent episodes of pouchitis that is responsive to antibiotics, the guidelines recommend the use of probiotics to prevent recurrent pouchitis.[31] Specifically, there were 3 RCTs assessing the efficacy of De Simone formulation of multistrain probiotics for the prevention of recurrent pouchitis; a meta-analysis of these trials found an 87% lower risk of relapse over 12 months.[31] There is no recommendation regarding the use of probiotics to treat active pouchitis.

Postbiotics are composed of microbial components and metabolites to confer a health benefit. These include metabolites such as SCFAs and secondary bile acids. SCFAs are known to have anti-inflammatory benefits and improve barrier function. Butyrate, delivered as an enema preparation, has been trialed in UC, but most studies failed to show a treatment difference between SCFAs compared with placebo.[32] In this trial, 38 patients with distal UC were randomized to receive nightly butyrate enemas or saline. In this study, clinical improvement was noted in 37% of the butyrate-treated patients and in 47% of the placebo-treated patients. Secondary bile acids, which are the biproduct of microbial metabolism of primary bile acids, reduce inflammation in animal models; however, there is limited use in human IBD cohorts.[33]

Microbiome Interventions: FMT

FMT has become a widely utilized method to restore the entire microbial ecosystem and not just gut bacteria.

While traditionally this therapy was reserved for multiply recurrent *Clostridiodes difficile* infection (CDI), more recently it has been explored as a preventative strategy earlier in the treatment paradigm for this complication.[34] Additionally, there were initial concerns regarding potential IBD worsening when used to prevent recurrent CDI in patients with IBD. However, in a prospective study it was found to be safe and yields high cure rates,[35] with low rates of disease exacerbation following this initial concern.[36]

Studies of FMT in IBD for non-CDI indications have focused primarily on UC (Table 1). A systematic review of 10 RCTs concluded that FMT is effective for inducing clinical and endoscopic remission of mild-to-moderately active UC without a significant increased risk of adverse events.[36] There is a paucity of data on the use of FMT for maintenance of remission of UC after FMT. However, 1 trial noted maintenance of remission through week 56 among participants who achieved remission with FMT capsules after antibiotic pretreatment; this was not observed in patients not receiving further FMT after induction.[44] Another trial randomized 73 patients with mild-to-moderate UC to standard medical therapy or weekly FMT (derived from rural donors and delivered via a colonoscopy) for 7 weeks, combined with an anti-inflammatory diet.[45] Participants receiving FMT arm had significant high rates of both clinical and endoscopic remission at weeks 8 and 48.

The data in CD are much more limited, and this likely reflects the heterogeneous nature of CD and difficulty conducting trials in this population. A single RCT of 17 patients with active CD receiving corticosteroids randomized them to a colonoscopic FMT or a sham FMT.[46] At week 10, steroid-free clinical remission rates were numerically higher in the FMT group. Two trials of FMT for pouchitis using either a sham FMT[47] or autologous FMT[48] showed no benefit. A small pilot study in 10 patients with IBD with concurrent primary sclerosing cholangitis showed improvement of alkaline phosphatase in 3 of 10 patients.[49]

More recently, the Food and Drug Administration has introduced a new term, live biotherapeutic products. These are defined as biological products that contain live organisms applicable to the prevention, treatment, or cure of a disease, and are also being studied to treat UC. These differ from traditional probiotics in that there is a pharmaceutical expectation and they are intended to be used in a sick population. These are regulated as drugs and therefore have been through phase 2 and 3 studies.[50] Additionally, there is ongoing debate as to whether products that are donor derived should be termed "live biotherapeutic products" as the Food and Drug Administration has referred to donor-derived products as "fecal microbiota products" more recently. Two live biotherapeutic products, live-jslm (Rebyota) and fecal microbiota spores, live-brpk (VOWST), are now approved for the prevention of recurrent CDI,[51,52] with indications beyond CDI being the next frontier. In UC, the first trials of an investigational fecal microbiota product, SER-287, showed efficacy in a phase 1 trial but failed to meet endpoints in a phase 2b study.[53,54] VE202 is a synthetic (not donor-derived) bacterial consortium containing a mixture of spore-forming *Clostridia* strains[55] and is currently being evaluated in a phase 2 program for the treatment of biologic-naïve mild-to-moderate UC (NCT05370885). EXL01 is a single *F prausnitzii* strain that is currently evaluated in the maintenance of steroid-induced clinical response/remission in patients with ileal CD (NCT05542355). Other fecal microbiota products are in early-phase development for UC as well. This therapeutic area is rapidly evolving and holds much promise.

Diet

Diet and Risk of Incident IBD

Exposures early in life, the period of maximum vulnerability of the microbiome and developing immune system, modifies risk of IBD. In a systematic review of population-based studies, a history of being breastfed in infancy was associated with a lower risk of CD (odds ratio, 0.71; 95% CI, 0.59–0.85) and UC (odds ratio, 0.78; 95% CI, 0.67–0.91).[56] In an elegant study, Guo *et al*[57] examined diet at 1 year to examine association with future onset IBD in Swedish and Norwegian birth cohorts. Compared with infants with a low diet quality at 1 year (assessed using the Healthy Eating Index), children with high diet quality had a reduced risk of IBD (hazard ratio [HR], 0.75; 95% CI, 0.56–1.00). Specific food constituents associated with this included an inverse association with fish and vegetable intake, while intake of sugar-sweetened beverages was associated with a higher risk of IBD.

Much of the initial attempts at identifying dietary risk factors focused on macronutrients. In a prospective cohort of 170,805 women, a higher intake of long-chain n-3 polyunsaturated fatty acids (PUFAs) comprising docosapentaenoic acid, eicosapentaenoic acid, docosahexaenoic acid (0.72; 95% CI, 0.51–1.01), or a lower n-3/n-6 PUFA ratio was associated with reduced risk of UC.[58] Conversely, high intake of arachidonic acid, an n-6 PUFA, and the concentration of arachidonic acid in gluteal fat pad biopsies was associated with increased risk of UC (rate ratio, 4.16; 95% CI, 1.56–11.04).[59] Studies have also suggested that this association may be modified by host genotype, in particular polymorphisms at the *CYP4F3* and *FADS2* loci.[60] Initial evidence from both case-control studies and prospective cohorts suggested an inverse association between dietary fiber and risk of IBD. In an analysis of the Nurses' Health Study cohorts, women in the highest quintile of intake of dietary fiber (median of 24 g/d) had a lower risk of development of CD than those in the lowest quintile (HR, 0.59; 95% CI, 0.39–0.90). Adding nuance to the impact of fiber on risk of IBD is the potential differential effect by subtype of fiber. For example, in the Nurses' Health Study cohorts,

Table 1. Summary of Randomized Controlled Trials of FMT for the Treatment of Ulcerative Colitis

Study	n	Disease Activity for Inclusion	FMT Route	Number of Infusions	Dosage	Stool Donor	Comparator	Primary Endpoints	Follow-Up	Clinical Remission	Clinical Response
Moayyedi et al, 2015[37]	65	Mayo clinical score ≥4 and endoscopic score ≥1	Enema (50 mL)	6 (weekly)	50 g stool in 300 mL water	Unrelated donor	Water enema	Total Mayo score ≤2 and endoscopic Mayo = 0	7 wk	FMT group: 9/38, control group: 2/37, $P = .03$	FMT group: 15/38, control group: 9/37, $P = .16$ (≥3 decrease in total Mayo score)
Rossen et al, 2015[38]	48	SCCAI ≥4 and ≤11	Nasoduodenal (500 mL)	2 (weeks 0 and 3)	Minimum 60 g stool in 500 mL saline	Patient directed donor	Autologous stool	SCCAI ≤2- and ≥1-point decrease in Mayo endscopic score	12 wk	FMT group: 7/23, control group: 5/25, $P = .29$	FMT group: 11/23, control group: 13/25, P = NS
Paramsothy et al, 2017[39]	81	Mayo clinical score ≥4 and ≤10 and endoscopic subscore ≥1	Initial colonoscopy (150 mL) then enemas	40 (5 per week for 8 wk)	37.5 g stool in 150 mL	Mixed unrelated donors (3–7 donors per patient)	Saline enema	Steroid free total Mayo score ≤2, with all subscores ≤1, and ≥1-point decrease in Mayo endoscopic score	8 wk	FMT group: 11/41, control group: 3/40, $P = .02$	FMT group: 22/41, control group: 9/40, $P = .01$
Costello et al, 2019[40]	73	Mayo clinical score ≥3 and ≤10 and endoscopic subscore ≥2	Initial colonoscopy (150 mL) then enemas	3 (week 0 colonoscopy, 2 enemas week 1)	Colonoscopy 50 g stool in 200 mL saline and glycerol, enema 25 g stool in 100 mL	Mixed unrelated donors (3–4 donors per patient)	Autologous stool	Steroid-free total Mayo score ≤2 and Mayo endoscopic score ≤1	8 wk	FMT group: 12/38, control group: 3/35, $P = .03$	FMT group: 21/38, control group: 8/35, $P < .01$ (≥3 decrease in total Mayo score)
Brezina et al, 2021[41]	45	Mayo clinical score ≥4 and ≤10, left sided disease only	Enema (150–170 mL)	10 (5 in first week and once weekly for 5 wk)	50 g stool in 150 mL saline and glycerol	Unrelated donor	5-ASA enema	Total Mayo score ≤2 with no subscore >1 at week 12	1 y	FMT group: 12/21, control group: 8/22, 95% CI: −7.6%, 48.9%	FMT group: 15/21, control group: 12/22, $P = .35$
Crothers et al, 2021[42]	12	Mayo clinical score ≥4 and ≤10 and all subscores ≥1	Initial colonoscopy (120 mL) then daily colonoscopic FMT	1 (induction) + daily for 12 wk	1 g stool/2.5 mL in colonoscopy infusion, 0.5 g stool per FMT capsule	Mixed unrelated donors (2 donors for entire study)	Sham therapy	Safety and feasibility of long-term colonoscopic FMT maintenance therapy	36 wk	Colonoscopic FMT group: 2/6, placebo group: 0/6; 95% CI, = 0.38-infinity, P = .45	Colonoscopic FMT group: 3/6, placebo group: 1/6; 95% CI, = 0.42–21.20, $P = .55$
Fang et al, 2021[43]	20	Mayo clinical score ≥4 and ≤12	Colonoscopy (150 mL)	Once	50 g stool in 150 mL saline	Unrelated donor	Mesalamine or corticosteroid induction with mesalamine maintenance	Mayo score ≤2 with each subscore ≤1, Mayo endoscopic subscore ≤1 compared with baseline	24 mo	FMT group: 9/10, control group: 5/10, $P = .019$	FMT group: 10/10, control group: 10/10, $p = 0.000$ (compared with pretreatment)

Table 1. Continued

Study	n	Disease Activity for Inclusion	FMT Route	Number of Infusions	Dosage	Stool Donor	Comparator	Primary Endpoints	Follow-Up	Clinical Remission	Clinical Response
Haifer et al, 2022[44]	35	Total Mayo score ≥4 and ≤10 and endoscopic subscore ≥1	Oral capsule	24 capsules per day for 1 wk, 12 per day for 1 wk, 6 per day for 6 wk	0.35 g stool per FMT capsule	Unrelated donor	Placebo capsule	Steroid-free total Mayo score ≤2, all subscores ≤1, and ≥1-point reduction in endoscopic subscore	8 wk	FMT group: 11/15, placebo group: 5/20, $P = .005$	FMT group: 11/15, placebo group: 9/20, $P = .94$
Kedia et al, 2022[45]	66	SCCAI ≥3 and ≤9, UCEIS . 1	Colonoscopy (200–250 mL)	Once	50 g stool in 200–250 mL saline	Mixed unrelated donors (2–5 per patient)	Standard medical therapy	SCCAI <2 and UCEIS <1	48 wk	FMT group: 21/35, SMT group: 10/31, $P = .02$	FMT group: 23/35, SMT group: 11/31, $P = .01$

Values are n/n, unless otherwise indicated.
CI, confidence interval; FMT, fecal microbiota transplantation; SCCAI, simple clinical colitis activity index; SMT, standard medical thearpy; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

an inverse association with CD was stronger for fiber intake from fruits, while fiber intake from whole grains, legumes, or cereal was not associated with modified risk.[61] Different sources and subtypes of fiber may differ by solubility of fiber, fermentation potential, and content of other potentially bioactive constituents such as polyphenols. There are less consistent data on the association between other macronutrients and risk of IBD. An analysis of the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort showed an increase in risk of IBD with higher intake of animal (but not plant) protein.[62]

Studies have also examined the association between dietary micronutrients and risk of IBD. An increase in intake of dietary zinc was associated with reduced risk of IBD within the Nurses' Health Study cohorts,[63] an association mechanistically supported by a beneficial impact of zinc on epithelial barrier in experimental models. While in experimental studies, oral iron was associated with a proinflammatory effect, and this association has been less robustly found in human cohorts with variable to null association between dietary iron or heme intake and risk of IBD.[64] Antioxidants in diet may play a role in modifying inflammation. In a study by Lu et al,[65] flavones and resveratrol in the diet were associated with a reduced risk of CD. Food additives may also play a role in the pathogenesis of IBD. In the Nurses' Health Study cohorts, compared with participants with low ultra-processed food (UPF) consumption, those in the highest quartile of intake had an increased risk of CD (HR, 1.70; 95% CI, 1.23–2.35)[66]; however, an association with risk of UC was not found. Specifically, ultraprocessed breads and breakfast foods, sauces, cheeses, spreads, and gravies showed the strongest association with CD risk.

Food is consumed within the context of other dietary items, and consequently, dietary patterns may be more relevant in informing dietary strategies for the prevention and treatment of IBD, rather than individual food group association. In a prospective cohort of 83,147 Swedish men and women, adherence to a Mediterranean diet pattern (MDP) was associated with a lower risk of CD (HR, 0.42; 95% CI, 0.22–0.80) but not UC.[67] An empiric inflammatory dietary potential (EDIP) derived from the association of foods with inflammatory cytokines in the serum was associated with a 51% higher risk of CD (HR, 1.51; 95% CI, 1.10–2.08) in 2 prospective cohorts.[68] Interestingly, compared with participants who were in the lowest tertile of EDIP score at baseline who subsequently moved to the highest tertile 8 years later, there was a 2-fold increase in relative risk of CD (HR, 2.05; 95% CI, 1.10–3.79), although the inverse diet, a reduction in risk on change from a high to low EDIP score, was not observed.

Diet and Disease Course

There have been fewer studies examining dietary risk factors for disease relapse or other outcomes. Two

studies suggested that increased red meat intake was associated with higher risk of disease flares in patients with UC, while 2 others did not find such an association.[69,70] In the PREDiCCt (Prognostic Effect of Environmental Factors in Crohn's and Colitis) study that followed 520 patients with UC (and 497 patients with CD), patients with UC in the highest reported meat intake had a 2-fold increase in risk of flares compared with those in the lowest category.[70] In contrast, in an Internet-based trial of red meat intake in the IBD Partners cohort, consumption of 2 or more servings of red meat per week was not associated with an increased risk of disease flares.[69] Similarly, there are inconsistent data on whether dietary fiber may play a role in preventing relapse. Two studies showed an inverse association between fiber intake and risk of IBD relapse, while 2 studies found no benefit and 1 study demonstrated an increase in risk of disease flares with high fiber intake.[71,72] There are several potential explanations for these divergent findings. First, studies of association of fiber intake and relapse are observational, and regular flares may alter dietary intake, rather than the other way around. This could also be explained by differences in source and subtypes of fiber as highlighted previously. In addition, an individuals' microbiome may influence their ability to process fiber and generate biologically active metabolites, leading to biology-dependent heterogeneity in effect.[73] Finally, studies have also highlighted the generation of beneficial SCFAs from fermentable fiber may be based on inflammatory status, leading to differing effects on the microbiome and metabolome based on presence of active disease.[74] Diet may influence outcomes beyond disease relapse alone. Godny et al[75] found that a low intake of fruits was associated with increased occurrence of pouchitis. Mechanistically, fruit consumption was associated with a favorable microbial profile, and influences abundance of *Faecalibacterium*, *Lachnospira*, and *Ruminococcus*.

Diet in the Treatment and Maintenance of IBD. Patients with IBD are often very keen to attempt dietary approaches for the induction and maintenance of remission, and doctors and dietitians should use evidence-based practice when advising and supporting patients through dietary management (Figure 2).

Exclusive Enteral Nutrition. The most widely investigated dietary intervention in IBD is exclusive enteral nutrition (EEN). This involves the oral or enteral delivery of nutritionally complete formula as a sole source of nutrition for 4 to 8 weeks with the exclusion of all foods and drinks, with some regimens allowing some clear fluids. EEN has largely been examined as treatment for active disease with evidence of benefit for CD but not for UC. A Cochrane review of 10 trials comparing EEN with corticosteroids showed greater benefit in pediatric than adult CD, and in per-protocol over intention-to-treat analysis (Table 2).[76] In 2 pediatric trials, there was no difference in remission rates between EEN and corticosteroids on intention-to-treat analysis; however, on per-protocol analysis (excluding children who could not complete treatment due to poor palatability or lack of acceptance of a nasogastric tube), EEN (89%) resulted in superior remission rates compared with corticosteroids (61%). In view of these findings, EEN is often first-line treatment in pediatric CD, as it also spares children from early-life corticosteroid exposure. Attrition from EEN therapy is high in both research and clinical practice[76] and is frequently due to issues of palatability, inability to consume the volumes required, and/or tolerance of a nasogastric tube. Identifying responders and nonresponders to EEN could better target who should be offered this therapy. A recent study showed EEN responders had higher gut microbiota richness and lower stool acetate and butyrate, with a multicomponent model incorporating microbiome, metabolome, diet, clinical, and immunological data predicting response to EEN with 78% accuracy.[77] In view of poor tolerance to EEN, attempts have been made to circumvent its use through dietary management approaches that partially (eg, CD exclusion diet [CDED]) or totally (CD-TREAT) replace EEN with normal foods. Despite the established efficacy of EEN or EEN-based diets, certain paradoxes remain unexplained with this treatment option. The microbial changes induced by EEN such as reduced diversity contradict the prevailing view of a healthy microbiome. In addition, EEN formulations have a high content of additives, which contrasts with therapeutic diets that attempt to minimize additive- and emulsifier-containing foods.[78] Further research is required to examined whether this is influenced by variation in biologic effect by type of additive.

CD Exclusion Diet. The CDED restricts a range of foods including dairy products gluten, baked goods and breads, processed meats, animal fats, canned/packaged products, emulsifiers, and other food additives.[79] The mechanistic rationale was based on in vitro and animal evidence of a possible impact on the gut microbiome and gut permeability.

Numerous uncontrolled clinical evaluations have been performed, but the most significant study was a randomized comparative trial of CDED as an adjunct to partial enteral nutrition compared with EEN in 74 children with active CD.[80] After 6 weeks, the primary outcome of tolerance was higher following CDED and partial enteral nutrition (97.5%) than EEN (73.7%) ($P = .002$), but there were no differences in clinical outcomes including clinical response and remission. At 12 weeks, during which phased reintroduction of normal foods occurred in the EEN group, the CDED plus partial enteral nutrition group had higher rates of sustained remission than the former EEN group.[80] In another randomized comparative trial, CDED plus partial enteral nutrition was compared with CDED alone in 40 adults with active CD.[81] There were no differences in the primary outcome of remission at 6 weeks between CDED plus partial enteral nutrition (68.4%) and CDED (57.1%) ($P = .4618$), nor were there any differences in response

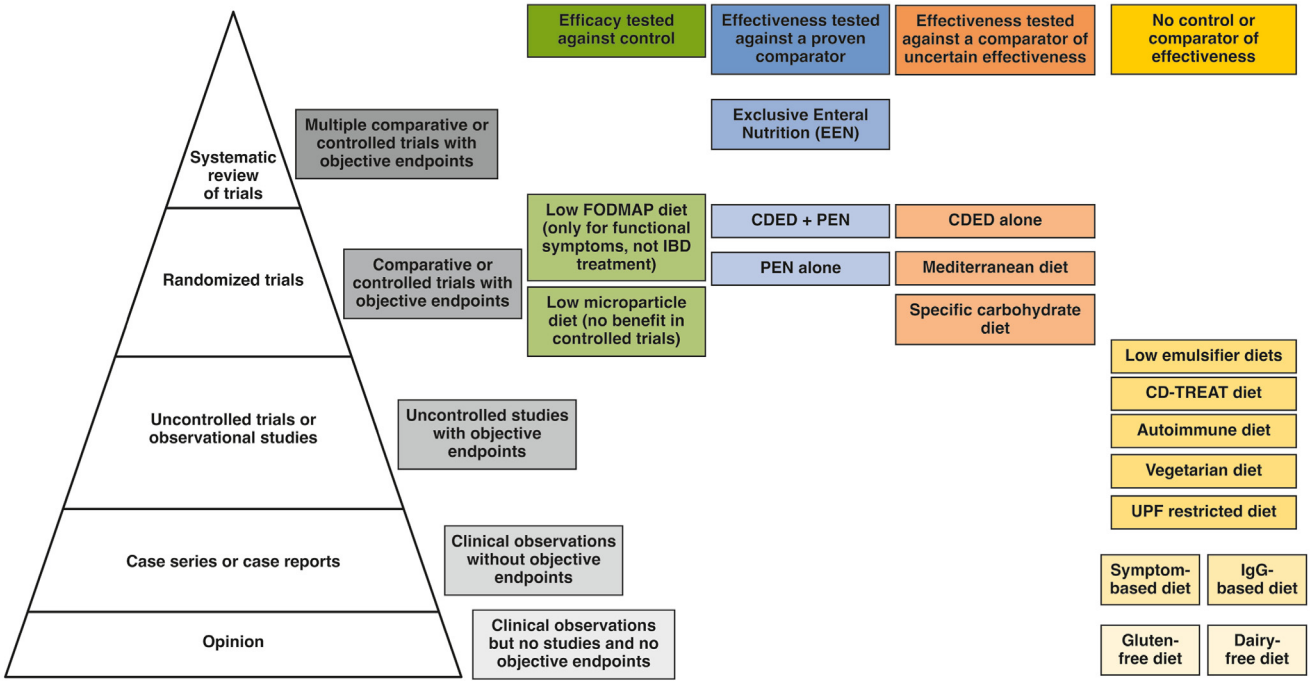

Figure 2. Evidence ladder for studies that have tested the efficacy or effectiveness of diet in the management of IBD. The hierarchy defines the levels of evidence used in evidence-based practice and is adapted here specifically for trials of diet in IBD including the use of objective inflammatory endpoints. Few randomized controlled trials have been conducted to demonstrate efficacy due to the challenges of control diet interventions (green). More randomized comparative trials have been conducted that compare diet with another intervention that is proven to be effective (blue) or with an intervention with uncertain effectiveness (orange). Many diets have not been tested in clinical trials with control or comparator groups and are based on uncontrolled trials, observational studies, case series, or case reports or opinion (yellow). PEN, partial enteral nutrition.

or remission at any of the time points (6, 12, or 24 weeks).

Other Therapeutic Diets. Several other diets have been examined as therapeutic options for the management of CD. The CD-TREAT diet was developed to replace EEN by mimicking the effect of enteral formulas with everyday foods, and therefore the diet excludes gluten, lactose, and alcohol and restricts starches and fiber to better match the profile of commercial formulas. The CD-TREAT diet was tested in 25 healthy adults and in HLA-B7 B27 transgenic rats, showing moderate-to-strong correlation for changes in both operational taxonomic units and genera between CD-TREAT and EEN.[82] In a pilot study in 5 children with active CD, 4 completed an 8-week treatment with CD-TREAT, all of whom entered remission, with statistically significant reductions in disease activity scores and fecal calprotectin.[82] In the Diet to INducE Remission in Crohn's disease (DINE-CD) study of mildly symptomatic patients with CD, an MDP (high in fruits, vegetables, legumes,

Table 2. Summary of Findings From the Cochrane Meta-Analysis of Clinical Trials of EEN vs Corticosteroids for the Induction of Remission During the Treatment of Active Crohn's Disease

			Remission Rate			
	Analytical Approach[a]	Trials/Patients	EEN	Corticosteroids	Risk of Remission in EEN	*P* Value
Children	Intention to treat	2/57	83 (24/29)	61 (17/28)	1.35 (0.92–1.97)	.13
	Per protocol	2/55	89 (24/27)	61 (17/28)	1.43 (1.03–1.97)	.031
Adults	Intention to treat	6/352	45 (87/194)	73 (116/158)	0.65 (0.52–0.82)	.0002
	Per protocol	6/307	58 (87/149)	73 (116/158)	0.82 (0.70–0.95)	.0092
All patients	Intention to treat	8/409	50 (111/223)	72 (133/186)	0.77 (0.58–1.03)	.08
	Per protocol	8/362	63 (111/176)	72 (133/186)	0.93 (0.75–1.14)	.47

Values are n, % (n/n), or risk ratio (95% confidence interval). Data were extracted from Narula et al.[76]

[a]Intention-to-treat analysis included all patients who started the trial. Per-protocol analysis excluded treatment failures due to poor palatability or lack of acceptance of a nasogastric tube (other treatment failures still included).

nuts and fish) resulted in symptomatic improvement in nearly half the individuals and resulted in improved in C-reactive protein or fecal calprotectin in up to a third of patients with elevated levels at baseline. In a prospective trial of 28 patients with quiescent UC treated with the MDP or control Canadian habitual diet for 12 weeks, a smaller fraction of patients in the MDP arm (20%) had elevated fecal calprotectin at the end of the study compared with the Canadian habitual diet (75%).[83] In addition, the MDP induced several favorable alterations in the gut microbiome. A 6-month open-labeled intervention with an anti-inflammatory diet (AID) designed to increase dietary fiber, antioxidants, and n-3 PUFAs while reducing red meat, processed meat, and sugar in patients with UC in clinical remission resulted in a lower fraction of relapse and larger fraction with normal fecal calprotectin at the end of the intervention in the AID group.[84] Other variations of the anti-inflammatory diet[85] and autoimmune protocol diets[86] have also demonstrated symptom improvement in case series but lack rigorous clinical trial evidence in support of efficacy. A dietary strategy to reduce hydrogen sulfide production (4-SURE [4 Strategies to Sulfide REduction]) diet was tolerable and acceptable in 28 adults with UC, with clinical response in nearly half the patients (46%) and endoscopic improvement in one-third (36%).[87] The diet was accompanied by an elevation in fecal SCFA content.

Specific Carbohydrate Diet. The specific carbohydrate diet (SCD) was developed 100 years ago and aims to restrict disaccharides and polysaccharides that are incompletely or completely unabsorbed in the gastrointestinal tract and are available for microbial fermentation. The diet excludes grains, sugars, and milk products, although it is incompletely defined, with inconsistencies such as fruits and vegetables being permitted despite being rich sources of polysaccharides. The mechanistic rationale for the SCD is not fully evidenced, and until recently, clinical evidence for the SCD was limited to case series, until the publication of 2 clinical trials. The first was a randomized comparative trial comparing SCD, a modified SCD protocol, and a whole food diet for 12 weeks.[88] Of the 18 children with active CD who enrolled, only 10 completed the study, all achieving clinical remission.[88] More recently, the previously described DINE-CD study compared an SCD with an MDP in 194 adults with mild/moderate symptoms of CD.[89] At 6 weeks, there was no difference in the primary outcome of symptomatic remission (SCD 46.5% vs MDP 43.5%), fecal calprotectin, or CRP response. The lack of control group limited the ability efficacy to infer effectiveness of either diet. Most clinical studies of SCD did not mandate significant objective inflammation at inclusion, and while biomarkers were measured at follow-up, the primary clinical outcome was not contingent on demonstrating resolution objectively of inflammation. Thus, while there is evidence of symptom benefit with SCD, to what degree this is accompanied by resolution of objective inflammation remains to be robustly established.

UPFs and Food Additives. Most therapeutic diets in IBD, CDED, CD-TREAT, MDP, or SCD, advise on the restriction of processed foods as part of other dietary restrictions; thus, the effect of UPF restriction alone cannot be ascertained. In addition, such trials did not quantitatively measure UPF intake. Food additives are substances intentionally added to food for a technological purpose and some, including emulsifiers, sweeteners, and colorants, have been shown to modify the microbiome and impact epithelial integrity in animal models.[90] Research in people with IBD has only been conducted for emulsifiers, albeit in small clinical trials. A crossover trial in 7 patients with quiescent UC demonstrated carrageenan supplementation did not induce gut symptoms,[91] while a resupplementation trial in 12 patients with UC showed carrageenan-restricted diet reduced relapse rates,[92] and an uncontrolled trial in CD showed restriction of all emulsifiers improved gut symptoms in 20 people.[93]

Low FODMAP Diet. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) are incompletely digested carbohydrates, some of which increase small intestinal water or colonic gas production. Temporary dietary restriction of FODMAP, followed by staged reintroduction to tolerance, is termed the low FODMAP diet and has been extensively studied in irritable bowel syndrome. An RCT in 52 people with IBD demonstrated the low FODMAP diet reduced bloating, flatulence, and stool frequency compared with a sham diet.[94] Importantly, the low FODMAP diet should not be used to treat active inflammation in IBD, but rather to manage burdensome gut symptoms in the absence of active disease.

Translation of Diet and Microbiome Interventions: Challenges and Opportunities

There are many common challenges to translating diet- and microbiome-based interventions in IBD and opportunities to stream-line interventional studies.

1. Defining mechanism of action: Unlike small molecules and biologics in which the precise immunologic target is clearly known, the biologic mechanisms of influence of both diet- and microbiome-based interventions are less well defined. Unlike measurable drug levels, at this time, there are also no reliable measures to quantify pharmacokinetic effect of diet- or microbiome-based interventions. This impedes identification of an effective dose, optimizing treatment, or monitoring biologic effect. There is an important need in the field for the development of quantitative biomarkers that can measure the biologic impact of these interventions to help precisely develop such interventions.
2. Biologic heterogeneity and personalization: There is wide heterogeneity in an individual's

microbiome composition, impacted by geography and environment, in addition to host factors. Beyond that, there is significant interindividual variability in microbial composition, and within the same individual at different time points. This challenges both the effectiveness and interpretation of microbiome-based intervention studies. Similarly, there is also differential susceptibility to dietary interventions that may be influenced by host genetics (gene-diet interactions) or underlying microbial composition (as has been identified for weight loss interventions). A more robust definition of the parameters contributing to this heterogeneity can help more precisely target the treatments to the subgroup most likely to benefit.

3. Manufacturing and regulatory hurdles: The regulatory path for microbiome-based interventions continues to evolve, with significant heterogeneity in regulations between different countries. This has hampered intervention trials across regions internationally. Similar variability in dietary practices across different populations may affect the effectiveness (or acceptability) of dietary interventions. There is also the need for efficient and scalable production of both diet- and microbiome-based interventions and a reproducible and consistent way to deliver such interventions. For microbiome interventions, it may be important to deliver it to the most appropriate region of the gut for benefit. For both dietary and microbiome interventions, it is important to precisely quantify all components of the intervention, particularly for mixed consortia or whole food diet-based treatments.

4. Optimizing robust clinical trial design: An important challenge in studies of microbiome- and diet-based interventions is patient selection and study design. Most studies of these interventions have focused on mild-to-moderate CD or UC; thus, it is unclear if such interventions (as opposed to immune-directed therapy) may have a role in those with more severe disease. Diet is a challenging intervention to investigate. It is difficult though not impossible to design "control" interventions, and controlled trials are therefore rare. Comparative trials of diet are often used to inform the best options for clinical practice; however, a trial of 2 diet interventions that does not show differences do not prove efficacy of either and does not prove equivalence unless the study was powered for equivalence analysis. Use of multidisciplinary teams with members with expertise in delivering dietary interventions and maximizing adherence is important to optimize success of such interventional trials. Assessment of adherence also relies primarily on self-report. It is important for research on objective biomarkers that could measure both adherence to dietary interventions as well as quantify their health impact, accounting for heterogeneity by individual biology. Studies have also frequently used subjective criteria for entry and as an endpoint. To generalizably inform their role in the therapeutic algorithm, it is important to have meaningful objective biomarker- and endoscopy-based endpoints to quantify effectiveness. It is important to examine them as both single and combination (along with conventional treatment) interventions, for varying durations of treatment, and both for induction and for maintenance of remission. Finally, it is likely that trial designs currently used to assess the efficacy of immunosuppressors are not optimal for evaluating microbiome- and diet-based interventions, and there is a need for innovation in this regard.

Conclusions

The external environment, through diet, and the internal gut microenvironment through the microbiome, play a central role in the development and propagation of IBD. While large prospective cohort studies have informed dietary risk factors prior to disease onset, there remains an important need to identify how diet influences established disease contributing to relapse or disease progression. Cross-sectional studies of well-phenotyped cohorts have provided important insights into the microbial architecture of IBD, but further work is necessary to identify longitudinal trajectory of the microbiome in relation to key disease outcomes. Dietary and microbiome-based treatments offer considerable promise in the management and potentially the prevention of IBD. High-quality interventional studies are required in well-characterized populations to inform the positioning of these treatments within our therapeutic algorithm.

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Conflicts of interest
The authors disclose the following: Harry Sokol has received lecture fees from, served on the board for, or served as a consultant for AbbVie, Adare, Amgen, Biocodex, Biogen, Bledina, Bromatech, Celltrion, Ferring, Fresenius, Galapagos, Immusmol, IPSEN, Jannsen, Lilly, Mayoli, MSD, Nestlé, Sanofi, Servier, Takeda, Tillotts, Urgo, and Viatris; owns stock in Enterome Bioscience; and is co-founder of Exeliom Biosciences. Jessica R. Allegretti has served as a consultant for Janssen, Pfizer, AbbVie, Finch Therapeutics, Seres Therapeutics, Ferring, GSK, Merck, Bristol Myers Squibb, Roivant, and Adiso; received grant support from Pfizer, Janssen, and Merck; and served as a speaker for BMS, AbbVie, and Janssen. Kevin Whelan has received research grants from Almond Board of California, Danone, and the International Nut and Dried Fruit Council; has received speaker fees from Danone; and is the holder of a joint patent to use volatile organic compounds as biomarkers in irritable bowel syndrome (PCT/GB2020/051604). Ashwin N. Ananthakrishnan has served on the advisory board for Geneoscopy.

The IBD Clinic of Tomorrow: Holistic, Patient-Centric, and Value-based Care

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There is increasing recognition of the associated bidirectional impact of inflammatory bowel disease (IBD) on patient well-being and the potential benefit of multidisciplinary teams to address these unique needs. At certain IBD centers, there has been an evolution towards patient-centric, holistic care to enhance well-being and improve health-related outcomes. Multiple models, incorporating various disciplines, care modalities, digital tools and care delivery, and resource support have arisen in IBD. Although most IBD centers of excellence are now incorporating such multidisciplinary care models, many practices still practice IBD-limited specialty care, limiting evaluations and interventions to the IBD itself and its direct consequences (eg, extraintestinal manifestations). In this piece, we seek to review the evolution of IBD care towards a patient-centric, holistic model (termed 360 IBD Care) including the role and impact of digital health tools, monitoring, and delivery in IBD, and a shift towards value-based care models with discussion of payor priorities in IBD. We also suggest potential opportunities for IBD practitioners to incorporate elements of holistic care on a local scale. Together, we hope such care models will enhance not only IBD-specific health outcomes, but also improve the general well-being of our patients with IBD today and tomorrow.

Keywords: Digital Health; Holistic Care; Multidisciplinary Care; Social Determinants of Health; Telemedicine; Value-based Care.

Inflammatory bowel diseases (IBDs) are chronic, inflammatory conditions primarily affecting the gastrointestinal tract, but with unique systemic issues. IBD can affect the entire age spectrum and is associated with significant morbidity and impaired quality of life. These impairments stem not only from symptoms or complications of active disease, but also from emotional, societal, economic, employment, and interpersonal challenges faced by individuals with IBD.

Historical specialty care for patients with IBD focused on management of the biological gastrointestinal disease and extraintestinal manifestations related to the systemic processes, limiting discussion of psychosocial factors or other domains impacting health outcomes.[1] Over the past few decades, research has highlighted the diminished health-related quality of life many individuals with IBD experience and identified factors negatively influencing disease experience. These include disease severity, mental health, chronic pain, opioid use, social, and economic factors.[2,3] There is growing recognition that addressing both biological and psychosocial factors influences disease, health, and well-being outcomes in IBD, particularly early in the IBD course.[4–7] Clinical programs integrating psychosocial care represents a step towards a more patient-centered, holistic approach to help patients with IBD, termed "360 IBD Care." We herein describe the critical aspects of such an encompassing model of care, including pertinent clinical focus points that drive health care outcomes in IBD, clinical personnel and responsibilities, incorporating digital tools, and moving towards value-based care through 360 IBD Care.

Key Components of 360 IBD Care

Evidence-based IBD Care

The foundation of successful 360 IBD Care is modern, individualized, and evidence-based disease care. IBD is heterogeneous with a broad spectrum of disease presentations, responses to therapy, and disease trajectories. Timely disease identification, risk-stratification, and agent selection is critical to achieving early disease control, which may influence disease trajectory.[8–10] Optimizing therapy and minimizing medication-related adverse events may help improve therapeutic benefit and durability. Treat-to-target monitoring to ensure and maintain disease control is the standard of care in IBD,[11] given the risk of disease-, therapy-, and extraintestinal-related complications, multidisciplinary management incorporating necessary medical and surgical specialists.

Abbreviations used in this paper: **EMR, electronic medical record; IBD, inflammatory bowel disease; SDOH, social determinants of health.**

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Mental Health Evaluation and Treatment

Patients with IBD experience higher rates of behavioral health conditions, including anxiety (1 in 3 patients with IBD) and depression (1 in 4 patients), compared with their non-IBD peers.[12] This interaction is likely bidirectional.[13,14] In addition to comorbid mental health disorders, other common concerns affecting well-being include fatigue, as high as 54% during remission and 76% with active disease,[15–17] and chronic pain, affecting up to 50% of patients with IBD.[18]

Given the prevalence and impact of mental health conditions on disease experience and outcomes in IBD, identifying and addressing such issues are critical to optimizing patient outcomes. The most established model integrating behavioral health specialists into clinical care settings is the collaborative care model, defined as a structured intensive coordination of care between medical and behavioral clinicians. The collaborative care model is supported by randomized clinical trials and a Cochrane review and meta-analysis demonstrating benefit over usual care to reduce the impact of behavioral factors on health for both short and long-term outcomes.[19] Specific to IBD, integration of a gastrointestinal-specific behavioral health clinician into the IBD practice improves patient uptake and intervention success.[20] Furthermore, as many as three-quarters of patients with IBD desire such behavioral evaluation as part of their routine IBD care, emphasizing the patient perspective on this need.[1]

However, integrating such behavioral infrastructure is not available to most gastroenterologists. Simple screening, identification, and acknowledgement of an existing mental disorder, with appropriate referral, can result in significant improvement in outcomes for many practices and is supported by multiple professional societies and patient foundations.[5,21–23] Adjunctive provision of self-management resources can also be considered. Additional screening for chronic pain and fatigue may help identify additional commonly encountered entities. Validated and easy to implement and interpret tools exist such as the Patient Health Questionnaire (PHQ), Hospital Anxiety and Depression Scale (HADS), and Generalized Anxiety Disorder-7 (GAD-7) (Supplementary Figures 1 and 2).[24–26]

Assessing Social Determinants of Health

There are many key social determinants of health (SDOH) factors that are routinely experienced by patients with IBD influencing disease experience and outcomes.[27–29] Frequently encountered IBD-related SDOHs include insurance access and coverage, medication access, costs of testing and procedures, transportation, food security, and social support.[30,31] Experts have argued for addressing SDOH in IBD care at the point of clinical contact.[32] Thus, a holistic multidisciplinary model should also include assessments and attempts to minimize negative impacts of SDOH. Most directly, SDOH assessments would include asking patients about their SDOH during clinical interactions. Keeping a list of industry and local resources can also be a helpful tool. Ideally, incorporating a licensed social worker as part of the care team allows expert evaluation and intervention, as well as the dual role of a behavioral health counselor. Social workers can assist patients in connecting with resources (eg, food, housing, insurance, transportation), teach systems navigation, problem solving, and coping skills in efforts to better empower patients to manage health needs. A clinical pharmacist can provide significant assistance with medication access and adherence. Anecdotal experiences support the potential success of such approaches.[33,34]

Dietary and Lifestyle Therapy

Patients with IBD are at risk of malnutrition, micronutrient deficiencies, and disordered eating with associated negative impacts on clinical and surgical outcomes.[35–39] Although high-level data is emerging, clinicians frequently encounter such questions directly from patients. Thus, having familiarity and addressing these topics either proactively or reactively is likely to improve patient well-being. Inclusion of a registered dietician as part of 360 IBD Care allows for personalization of general dietary modification strategies, screening for and addressing malnutrition and micronutrient deficiencies, and assistance in managing severe malnutrition or IBD complications.

Emerging evidence has demonstrated significantly disorganized sleep habits and patterns in individuals with IBD, particularly in those with concurrent behavioral health conditions.[40–43] Thus, early identification of sleep disorders and proactive counseling on sleep hygiene in IBD may help improve well-being. Simple universal hygiene recommendations include maintaining regular sleep schedules, minimizing naps, avoiding stimulant substances and alcohol 4 to 6 hours before bed, and limiting screen time before bedtime and while in bed.

Health Maintenance

Individuals with IBD have unique health maintenance needs including vaccine administration, cancer screening, and bone health assessments.[22] Although specialists often view such interventions as the responsibility of a primary care provider, patients with IBD are often young and view their gastroenterologist as their primary health care provider. Guidelines now recommend that gastroenterologists take ownership of vaccine recommendations with shared responsibility of delivery/administration between primary care and pharmacy providers.[22] Checklists maintained by both the patient and the provider can be of great assistance.[23] However, given visit time restrictions for many gastroenterology providers, delegating completion of health

maintenance needs to an advanced practice provider or clinical pharmacist is an attractive and successful option.[44,45] Similarly, population health management tools, self-management support, and primary care provider education and direction can be helpful measures to address health maintenance needs.

Community vs Specialty IBD Care Evolution

Given the multidimensional needs of patients with IBD detailed above to achieve true holistic 360 IBD Care, there is a diverging ability to incorporate the appropriate personnel and resources to address the relevant domains between community practices and specialty IBD care. We recommend that all professionals who care for individuals with IBD familiarize and incorporate screening tools and strategies along with local resources for easy referrals when multidisciplinary care is not locally available (eg, https://romegipsych.org/ or the therapist finder tool at https://www.psychologytoday.com).

For IBD specialty clinics, the proactive evolution towards multidisciplinary, holistic care will likely expand upon historical expertise and clinical practice patterns. Integrating personnel with the clinical knowledge and focusing on multidimensional care in a collaborative, team-based approach to address the patient needs is critical. Prior work has suggested a framework for developing such "IBD medical homes," including ideal personnel such as: IBD gastroenterologist, behavioral health clinician, registered dietician, clinical pharmacist, licensed social worker, advanced practice providers, and nurse care coordinators (Supplementary Appendix).[46–48]

As routine IBD care continues to evolve into multidisciplinary care, we anticipate a similar evolution in the relationship between community and specialty practices. Historically referrals to specialty practices were often reserved for severe, refractory cases, disease- or therapy-related complication management, or second opinions at patient or provider request. We expect that specialty IBD centers will evolve away from such reactionary involvement towards more proactive, generalized, IBD population-based approaches. Such expansion will help disseminate multidisciplinary, patient-centric care to all patients with IBD either on a short-term or more sustained basis, depending on individual needs and risk, and hopefully alter the natural history of disease and associated health outcomes in IBD.[49] Models of this evolving relationship include IBD medical homes or neighborhoods, or hub-and-spoke models such as those employed by the Veterans Affairs system, Dartmouth Hitchcock Medical Center, and the Rural Advanced Practice Providers Delivering IBD Care in the US (RADIUS) program.[46,50,51]

Remote Monitoring and Between-visit Interactions

With a transition away from reactionary episodes towards more proactive, holistic IBD care, the role of digital innovation to enhance care monitoring and delivery is expanding. Traditional care and monitoring results in delays in care and inefficiency. The average office visit including travel and wait time is nearly 2 hours.[52] Telemedicine can improve access and monitoring and includes an array of applications and services, including 2-way patient-provider videoconferencing, teleconsultation between a distant and local provider, electronic messaging, and remote monitoring (Figure 1).

Telehealth in IBD Prior to COVID-19 Pandemic

Prior to the pandemic, virtual or telehealth visits in IBD were limited in scope. The University of Maryland, an early adopter of telehealth in IBD, reported that 83% of patient visits were uncomplicated, 71% patients noted shorter visit durations, 88% had all concerns addressed, and 94% desired future telehealth visits. Importantly, 84% of patients reported that they saved at least 1 hour with a virtual visit with over 40% saving more than 3 hours.[53] Similar results were reported by Dartmouth, another early adopter of telehealth.[54] A more recent study from Scotland demonstrated that virtual visits with an IBD specialist nurse resulted in avoiding 92% of in-person follow-up visits and over 70,000 km of travel distance saved.[55]

Shift to Telehealth in a Pandemic

Despite these encouraging preliminary results, adoption of telehealth was extremely low prior to the COVID pandemic. However, the pandemic completely changed how health care was delivered. A survey of over 800 providers from 56 countries reported a complete shift in visits, with less than 25% of visits occurring in the office. Of virtual visits, most were conducted over the telephone, although video visits occurred in 1 of 6 encounters with higher rates of video calls in the United States.[56] In the United States, several regulatory changes eased access, reduced regulatory restrictions, and improved reimbursement for telehealth.

Providers adapted well to the change, maintaining access to biologic therapy and visits for clinical trials, initiation of biologic therapy, and multidisciplinary care. However, the number of outpatient visits was reduced by 30%.[57] Vanderbilt Medical Center's study on telehealth during the pandemic ($n = 2571$) reported that only 1% of visits could not be completed with 88% including a video component. Predictors of failed virtual visits including older age, non-commercial insurance, and non-White race.[58]

Is Telehealth Here to Stay for Multidisciplinary Care?

As the pandemic eased, virtual visits utilization waned for a few reasons. First, most states again require

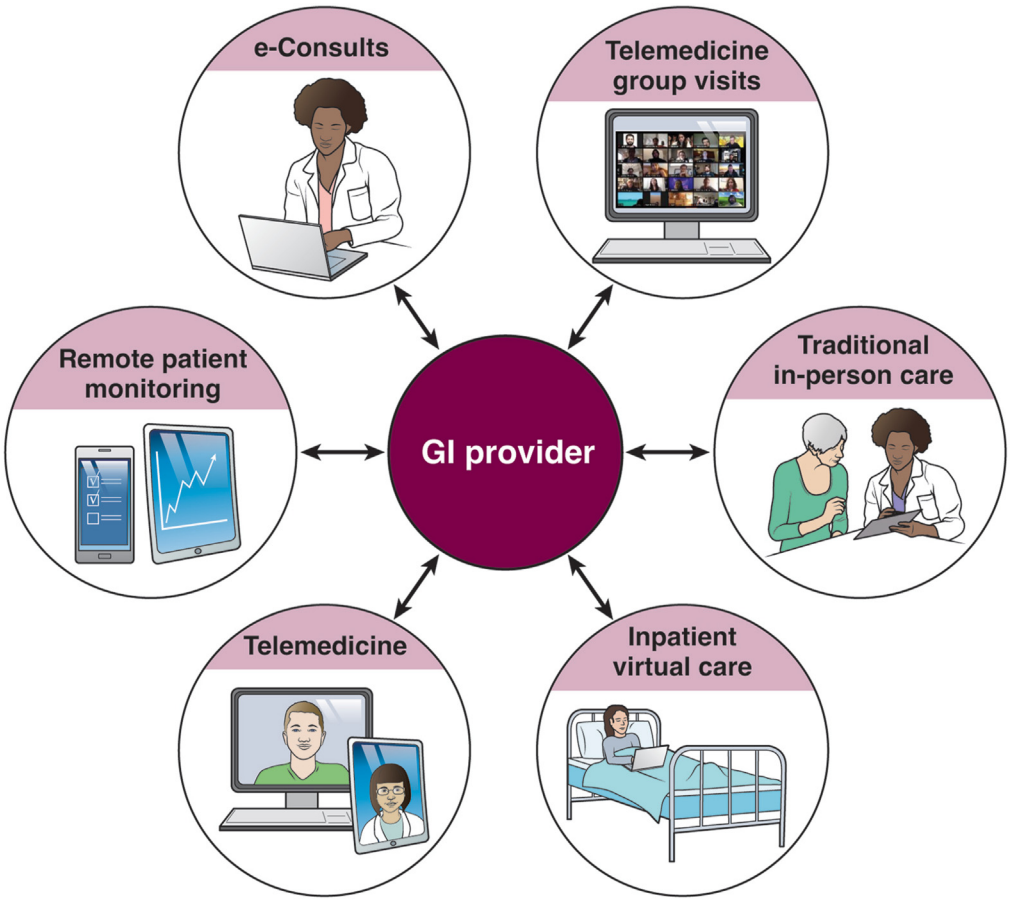

Figure 1. Various formats for virtual care in gastroenterology. From Gellad ZF, et al. Gastroenterology 2023;164:690–695.[82]

providers to have a license in the state the patient resides in during the visit. Prior to integration within the electronic medical record (EMR), scheduling virtual visits could be labor-intensive. Provider preference for in-person care also contributed. Other factors include the need to integrate multidisciplinary care in real time, loss of revenue for clinics in regulated space, and decreased point of care vaccinations and phlebotomy. Despite these limitations, telehealth still has a role in health care delivery in patients with IBD. It provides access flexibility and can decrease out of pocket costs for patients. Integration of pre-visit questionnaires and interconnecting other staff members requires collaboration with information technology specialists and enhanced coordination from support staff. Importantly, providers can also be reimbursed for telephone calls to patients. The precise ratio of in-person to virtual visits is not known but, in our experience, using these visits to provide continuity of care in stable patients and perhaps with a ratio of 1 in-person visit to 1 virtual visit seems reasonable.

Remote Monitoring in IBD

Remote monitoring has been studied more extensively. A randomized trial of a remote monitoring system called Constant-Care in patients with mild to moderate ulcerative colitis demonstrated better adherence to acute treatment, shorter relapses, and improved health-related quality of life in the remote monitoring arm over standard of care, although only 41% of patients completed the study. Although there were less acute and routine visits in the intervention groups, emails and telephone calls were higher.[59] A larger randomized controlled trial (n = 348) in the United States using text messaging technology for remote monitoring showed no difference in disease activity scores or health-related quality of life between groups, but IBD and non-IBD related hospitalizations were lower in the remote monitoring intervention groups compared with standard of care. Conversely, noninvasive diagnostic tests, telephone encounters, and electronic messaging were higher in the intervention arm.[53]

Project Sonar, a remote monitoring system developed by the Illinois Gastroenterology Group in collaboration with a large commercial payer, incorporates monthly patient-reported symptoms into the EMR and payer health care utilization system, with clinical staff reviewing "pings" and working with the provider to make management changes if needed. This system resulted in decreased hospitalizations, emergency room visits, and overall costs.[60–63] The largest study to date compared remote monitoring (MyIBDcoach) as a replacement to standard of care and included nearly 1000 patients from 2 academic and 2 community practices in the Netherlands. They demonstrated a significant decrease in office visits, hospitalizations, and costs without a

different in flares, steroid courses, surgeries, and quality of care scores.[64,65] A recent systematic review and meta-analysis demonstrated improved health-related quality of life and disease knowledge and decreased office and emergency room visits in patients using remote monitoring.[66] These results are encouraging and suggest that remote monitoring can be used as a partial replacement to in-person care or as a red flag technique to identify patients with IBD early in a flare.

Ideal logistical operations are still being determined. Integration within the EMR is critical. The optimal frequency of monitoring is not yet known, although less frequent interactions during remission with an option for on demand assessment is more likely to be accepted by patients.[67] An issue with remote monitoring is the party responsible for reviewing the results and implementing changes. Most studies utilized an IBD nurse to review results. Incorporating a provider will likely lead to increase in non-reimbursable work unless novel care models are developed.[68] More recently, several systems have implemented billing measures for certain more time-intensive portal-based messages and interactions, although provider uptake, patient satisfaction, and clinical impacts of this approach are uncertain.

The Payor and Value-based Care Models

Emerging IBD healthcare models such as 360 IBD Care rely on a team-based, multidisciplinary approach, and are moving towards payor partnerships around value-based care. Today, payors want cost predictability, cost savings, improved patient outcomes and satisfaction, and overall prevention of costly, severe disease. In theory, the IBD value-based care model would rely less on volume and consequent reimbursement via relative value units and more on quality and cost drivers that the health care team is able to control.[69] Financing the health care infrastructure and personnel required and being accountable for certain unpredictable costs (eg, biologics) are challenges to 360 IBD Care.

Value-based care initiatives, including the IBD medical home, remote monitoring platforms, and learning health care networks, have all shown success in improving care quality, patient outcomes, and reducing health care spending in some populations.[70] Additionally, value-based care models, including Accountable Care Organizations and bundled payments, are designed to incentivize health care providers to focus on the quality of outcomes rather than the volume of services provided.

The primary aim in IBD management under these models is to achieve and maintain long-term disease remission, prevent complications, and enhance the patient's health-related quality of life. In a value-based framework, providers managing a patient with IBD would be motivated to adopt a multidisciplinary approach to prevent exacerbations and reduce unplanned care (eg, hospitalizations and emergency department visits).[4,47]

Transitioning to value-based care in IBD involves addressing several intricate challenges. Key among these is the establishment of appropriate metrics and benchmarks that accurately reflect the complexity and multifaceted nature of IBD management. Benchmarks must account for the heterogeneity of the disease presentation and trajectories. This includes setting quality metrics such as hospitalization rates for disease exacerbation, the frequency of corticosteroid use as an indicator of uncontrolled disease, and the incorporation of patient-reported outcome measures that effectively capture the impact of the disease on health-related quality of life.

The adoption of these IBD value-based models are in a nascent stage, with a significant portion of health care payments still adhering to fee-for-service. The evidence supporting improvement in care through value-based models is emerging but, thus far, only with modest cost savings. In IBD, these savings could be substantial, considering the high costs associated with managing acute exacerbations and complications of the disease. Balancing these savings against improvements in patient-centric outcomes, such as disease activity scores and health-related quality of life assessments, is a critical aspect of value-based IBD care.[49]

The future of payor-provider value-based constructs in managing chronic diseases like IBD represents a transformative era in health care. As the United States health care system grapples with escalating costs, a collaborative approach between payors and providers is key, pivoting towards shared risk and savings models. This evolution, underpinned by sophisticated data analytics and health information technologies, such as artificial intelligence, will focus on holistic, patient-centric care.[71] The integration of these value-based models is poised to improve not just the efficacy of care and patient satisfaction but also to address health care disparities, ensuring equitable and effective treatment across diverse populations. This paradigm shift towards more integrated, data-driven, and personalized care is essential for the sustainability and effectiveness of health care systems in managing IBD (Figure 2).

Shifting Demographics in IBD and Future Needs

Despite the rapidly increasing incidence of IBD among non-White populations, nearly all clinical research on IBD populations is conducted in people of non-Hispanic, White, European descent.[72] Thus, there are significant knowledge gaps in underrepresented IBD patient populations.[73] Furthermore, underrepresented groups experience more challenges to access specialist IBD professionals, cost of care, medical trauma, stigma of mental health treatment, the use of complementary and alternative medications, mistrust of modern medicine, and fear of adverse medication effects.[74–76]

Figure 2. Characteristics of IBD centers evolving towards patient-centric, holistic care.

Similarly, as the population of patients with IBD ages, often having experienced higher disease complexity due to the lack of effective therapies at the time of diagnosis, there is a dire need to identify the role of the gastroenterology team in the management of non-GI comorbidities, polypharmacy, functional status, response to treatment, and well-being.[77] The elderly are navigating the growing complexity of the medical system, polypharmacy and comorbidity, and reduced access to effective medications and exclusion from industry-supported patient assistance programs when on governmental insurance programs, with psychosocial considerations like caregiver burden, social isolation and loneliness all contributing to outcomes.[78,79]

There is also likely to be a shift in the professionals who provide the needed 360 IBD Care. An impending shortage of gastroenterologists in face of increasing demand is anticipated over the next 2 decades. A clinical shift towards advanced practice providers is underway.[80] Clinical pharmacists are also increasingly recognized as critical to the management of IBD, given the complexities of therapeutic drug monitoring, medication adherence, shifting towards biosimilars, medical decision-making, health care maintenance, and health care transitions.[44] The dietitian focused on identifying and remediating malnutrition and fostering self-management skills through diet is of also growing importance.[81]

Finally there is growing support for: (1) the introduction of early, effective behavioral self-management training in complex IBD (eg, the Mount Sinai GRITT Program); (2) the creation of embedded gastropsychologist-led IBD programs (eg, Dartmouth, UChicago, Cleveland Clinic); (3) the multidisciplinary, skills-based facilitation of young adults transitioning to adult-centered care (eg, the PACE Program in Canada); and (4) the implementation of in-person, telemedicine, and digital behavioral health solutions with or without health coaching. Social workers will continue to serve as a lifeline in support of the ever-changing complexities of the health system and the increasing awareness of the SDOH on disease outcomes.

Conclusion

Management of inflammatory bowel diseases is costly, with a high impact on psychosocial needs and key gaps in social determinants of health. Patient-centric, holistic multidisciplinary care models are needed to optimize clinical outcomes and personal well-being. Optimal integration of multidisciplinary personnel, including costs and reimbursement, is evolving with a shift towards value-based alignment with payors, but significant hurdles remain. Remote monitoring and telehealth offer proactive and patient-oriented approaches to IBD care with potential cost-savings. Providers should continue striving for and adopting these concepts for local implementation to improve the care for patients with IBD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.04.042.

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Conflicts of interest
The authors disclose the following: Benjamin H. Click reports consulting for AbbVie, Bristol-Meyers Squibb, Janssen, Prometheus, Pfizer, Takeda, and TARGET-RWE. Raymond K. Cross reports advisory boards and consulting for Abbvie, Adiso, BMS, Fresenius Kabi, Fzata, Janssen, Magellan Health, Option Care, Pfizer, Pharmacosmos, Samsung Bioepis, Sandoz, Sebela, and Takeda; research grant from Janssen; member of the Executive Committee for the IBD Education Group; and Scientific Co-Director for the CorEvitas Registry. Miguel Regueiro reports advisory boards and consultant (both) for Abbvie, Janssen, UCB, Takeda, Pfizer, BMS, Organon, Amgen, Genentech, Gilead, Salix, Prometheus, Lilly, Celgene, Boehringer Ingelheim Pharmaceuticals Inc. (BIPI), Celltrion, and Roche. Laurie Keefer reports consultant to Pfizer, Coprata Health, and Trellus Health; research grant from Ardelyx; co-founder and equity owner in Trellus Health, a for-profit digital wellness company for inflammatory bowel disease; and Board of Directors Rome Foundation.

Supplementary Appendix

Ideal Personnel for 360 IBD Care Team

1. **Inflammatory bowel disease (IBD) gastroenterologist** familiar with the expansive impact and drivers of wellbeing in IBD, able to implement evidence-based IBD care with patient-centric evaluations and shared decision-making.
2. **Behavioral health clinician** such as a health psychologist or psychiatrist with experience in managing IBD-related disorders (eg, stress reduction and resilience-building, anxiety, depression, chronic pain, medical trauma and post-traumatic stress, smoking cessation).
3. **Registered dietician** with expertise in IBD-related dietary strategies, severe malnutrition, parenteral nutrition, with a focus on individualized dietary modifications to accommodate a patient-centered approach.
4. **Clinical pharmacist** with familiarity of IBD specialty medications and access, drug and disease monitoring paradigms, and health care maintenance recommendations.
5. **Licensed social worker** to evaluate and address key social determinants of health and provide behavioral counseling and support.
6. **Advanced practice providers** with similar expertise as the gastroenterologist to expand gastrointestinal provider access and ensure close monitoring and follow-up. Experience in gastroenterology, internal medicine, and infusion familiarity are helpful, but not required.
7. **Nurse care coordinators** to help harmonize the multidisciplinary care needs, implement, and follow-up on clinical care plans, monitor patients between visits, and provide a rapid access point for urgent patient needs. Experience in care coordination, program management, and population health can be greatly beneficial when available.

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Supplementary Figure 1. Hospital Anxiety and Depression Scale (HADS) screening tool.

GAD-7 Anxiety

Over the last two weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

Column totals _____ + _____ + _____ + _____ =

Total score _____

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Source: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD-PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues. For research information, contact Dr. Spitzer at ris8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc. Copyright© 1999 Pfizer Inc. All rights reserved. Reproduced with permission

Scoring GAD-7 Anxiety Severity

This is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all," "several days," "more than half the days," and "nearly every day."
GAD-7 total score for the seven items ranges from 0 to 21.

0–4: minimal anxiety

5–9: mild anxiety

10–14: moderate anxiety

15–21: severe anxiety

Supplementary Figure 2. Generalized Anxiety Disorder (GAD-7) screening tool.

How Artificial Intelligence Will Transform Clinical Care, Research, and Trials for Inflammatory Bowel Disease

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Artificial intelligence (AI) refers to computer-based methodologies that use data to teach a computer to solve predefined tasks; these methods can be applied to identify patterns in large multi-modal data sources. AI applications in inflammatory bowel disease (IBD) includes predicting response to therapy, disease activity scoring of endoscopy, drug discovery, and identifying bowel damage in images. As a complex disease with entangled relationships between genomics, metabolomics, microbiome, and the environment, IBD stands to benefit greatly from methodologies that can handle this complexity. We describe current applications, critical challenges, and propose future directions of AI in IBD.

Keywords: Artificial Intelligence; Computer-aided Diagnosis; Computer Vision; Crohn's Disease; Inflammatory Bowel Diseases; Machine Learning; Ulcerative Colitis.

Artificial intelligence (AI) refers to a group of computer-based methodologies that use data, such as text, images, video, or sound, to teach computers to solve predefined tasks such as prediction or categorization. The significant growth in the study of AI in medicine has emerged due to the collections of large multimodal (image, omics, text, video) datasets from the practice of medicine, computational hardware capable of processing and storing large volumes of data, and the increasingly sophisticated methods that use data to teach computers.[1] New computational tools are capable of modeling high-dimensional data, which can identify patterns in large datasets not easily discernable by humans or where a task is done excellently by humans but could be done faster by computers. Diseases like inflammatory bowel diseases (IBDs), which have entangled relationships between genomics, metabolomics, microbiome, and the environment, stand to benefit from methodologies that can handle this complexity.[2]

We will illustrate how AI is currently being applied to the landscape of IBD and hypothesize future directions for the field. Importantly, we will also detail critical challenges in the application of AI in IBD. Although we will not delve into the details of the multiple unique methods that comprise AI, there are excellent resources aimed at clinical audiences.[3–5] It is an exciting time for applied data science in medicine, but there are multiple critical unmet needs to realize the full potential of these methods in IBD.

AI Applications in Routine Patient Care and Clinical Interactions

Routine patient care is poised to be transformed using large language models (LLMs), which can understand and generate meaningful text and documentation. Automated patient documentation is a practical application of LLMs in clinical care. Several commercial voice-to-text solutions are recording patient-provider interactions and generating documentation, including Google Cloud Speech-to-Text, Amazon Transcribe Medical, Ambience, Nuance DAX, and DeepScribe.ai, helping reduce documentation and administrative burdens (Figure 1).[6] Although practical and timely, automated documentation highlights potential privacy risks related to mass collection of personal identifiable medical and social details.[7]

LLMs' ability to access and formulate diagnostic and treatment conclusions will pose a major change to how

Abbreviations used in this paper: AI, artificial intelligence; AUC, area under the curve; CD, Crohn's disease; CDS, cumulative disease score; CE, capsule endoscopy; EHR, electronic health record; GHAS, Global Histology Activity Score; GWAS, genome-wide association studies; IBD, inflammatory bowel disease; LLM, large language model; MaRIA, magnetic resonance index of activity; MES, Mayo endoscopic score; MRI, magnetic resonance imaging; pCLE, probe-based confocal laser endomicroscopy; PHRI, PICaSSO Histologic Remission Index; RCT, randomized placebo-controlled trial; RDI, Red-Density index; TNF, tumor necrosis factor; UC, ulcerative colitis.

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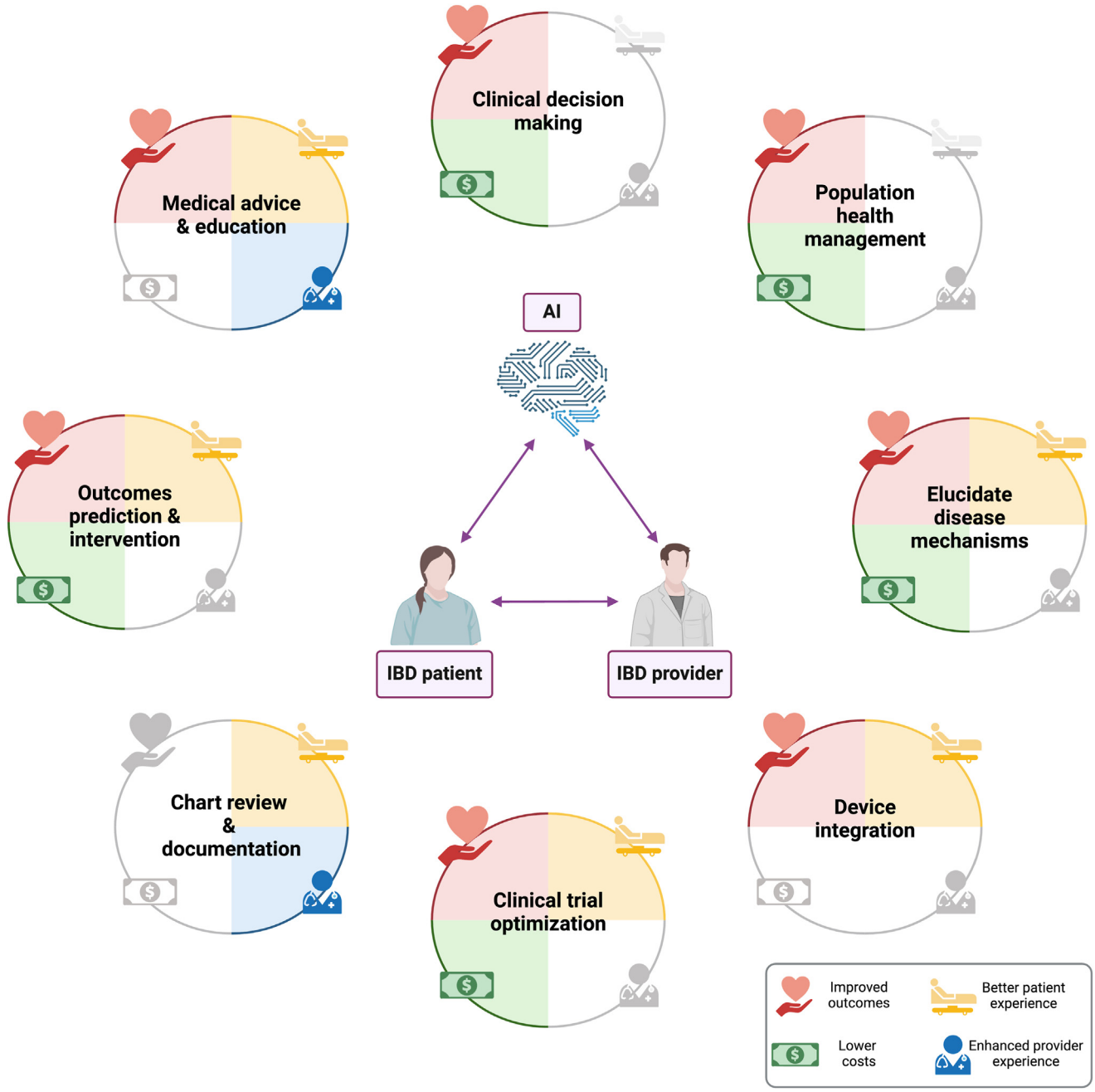

Figure 1. AI's hypothesized impact on multiple facets of IBD care and research.

we deliver care. Chatbots such as ChatGPT (OpenAI), Claude (Anthropic), and Med-PaLM (Google) enable both patients and providers to utilize LLMs for clinical decision-making (Figure 1). Current use of generative AI in IBD is limited to patient or provider questions regarding disease prognosis, tests, and treatment options. Although Chatbot answers to common patient questions are promising, randomness, limited reproducibility, and frank inaccuracy of responses remain.[8–10] Responses can vary over time, LLM platform, and even LLM versions, raising challenges for gauging utility and introducing potential liability for providers. IBD specialists will need to actively evaluate, guide, and oversee LLM model output to ensure safe equitable access to reliable medical information using these new means of information gathering.

Finally, the potential for LLM-based extensions to existing AI systems may automate the collation of disparate information in the electronic health record (EHR). An LLM extension to summarize endoscopic findings in the proper anatomical context and characterization, integrate other information about symptomatology from the provider-physician interaction, and features about patient history that may contraindicate specific therapies, could provide a global assessment to guide therapeutic management.

AI Applications in IBD Endoscopy, Radiology, and Histology

AI-aided Endoscopy in IBD

Endoscopy is a key tool for diagnosing and assessing IBD, aiming for mucosal healing as the primary treatment goal.[11] AI in IBD endoscopy has potential to objectively evaluate disease activity, predict outcomes, and address challenges of subjectivity, interobserver variability, interpretation of complex imaging technologies, and the overall quality of our assessments. AI provides a foundation for precision endoscopy, paving the way for improved IBD management in clinical trials and clinical practice (Figure 2).

Despite the importance of endoscopy, all standardized scoring instruments are hindered by subjectivity even when interpreted by experts.[12] Hence, several AI models applied to white light endoscopy (Supplementary Table 1) aim for a reproducible, swift, and standardized assessment for grading disease activity, with high overall accuracy and concordance with experts.[13–21] A recent systematic review and diagnostic test accuracy meta-analysis of 12 studies showed promising AI performance in evaluating mucosal healing in ulcerative colitis (UC).[22] AI exhibited high sensitivity and specificity, yielding predictable diagnostic odds ratios for fixed images (0.91, 0.89, and 92.42) and videos (0.86, 0.91, and 70.86). However, moderate-to-high heterogeneity (I^2 constantly over 90%) between studies limited the overall quality of evidence. Evidence is mounting, particularly for UC, that AI can approximate central reader performance for standardized endoscopic disease activity scoring.[18]

Using AI for Development of New Methods of Assessing IBD Endoscopic Activity

AI is helping to develop new strategies for IBD endoscopic assessment that may provide advantages over conventional standardized scoring. In recent work, Stidham et al leveraged video signal analysis to develop the cumulative disease score (CDS) to aggregate the total amount of mucosal injury over the length of the entire colon.[23] When applied to a phase III clinical trial of ustekinumab vs placebo, the CDS demonstrated nearly double the power to detect differences in mucosal healing compared with the Mayo endoscopic score (MES). In addition, the CDS also showed significantly better correlation with patient clinical response than the MES. Kuroki et al developed a novel AI system to assess vascular healing of mucosa in UC, reporting excellent separation of patients likely to relapse vs remain in remission within 12 months.[24] Similarly, groups exploring colormetric image analysis have developed the Red-Density index (RDI), which quantifies the number of red pixels in endoscopic videos. The RDI has been shown to strongly agree with standardized histologic scores and is showing promise as a predictor of 5-year clinical remission.[25,26] These results suggest that AI-powered

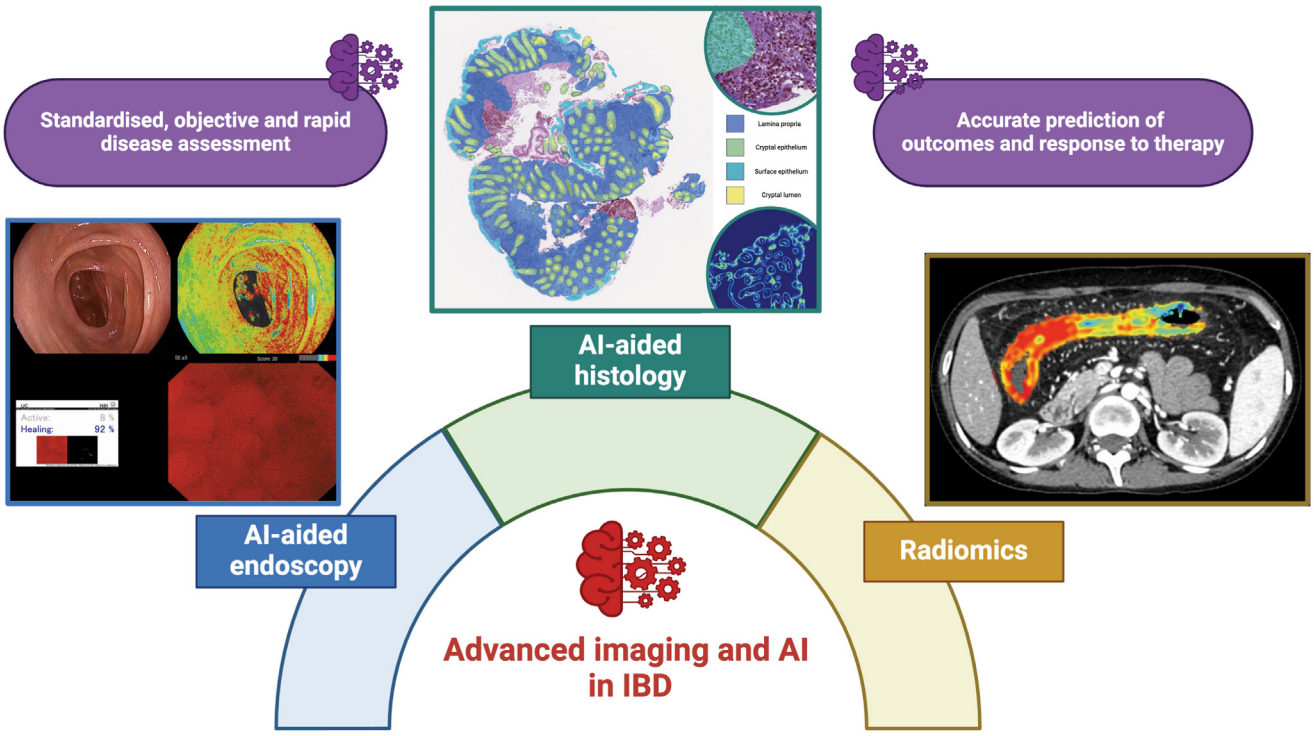

Figure 2. AI provides a foundation for precision endoscopy, paving the way for improved IBD management in clinical trials and clinical practice.

analysis of traditional endoscopy can outperform traditional IBD measures and may help predict clinical outcomes.

Using AI to Enable Routine Use of Advanced Endoscopic Imaging

AI is also helping improve our ability to standardize and interpret advanced endoscopic techniques.[27] An AI model of virtual chromoendoscopy images demonstrated a sensitivity of 79%, a specificity of 95%, and an area under the curve (AUC) of 0.94 for detecting endoscopic and histologic remission in UC.[28,29] Endocytoscopy high magnification imaging has been available for over a decade, although real-time interpretation of 520× magnification of mucosal tissue has proven challenging. Maeda et al introduced AI applied to endocytoscope, EndoBRAIN-UC (Cybernet System), showing an accuracy of 91% in predicting histological activity.[30] Vitali et al trained an AI model to classify the presence of histologic features, including crypt characteristics and neutrophils on endocytoscopic images in UC. The resulting ELECT score had very good correlation with the Robarts ($r = 0.70$) and Nancy ($r = 0.73$) histologic indexes, with a sensitivity and specificity for active disease of 88.0 and 95.2%, respectively.[31] Several other groups have also developed computer-based models using probe-based confocal laser endomicroscopy (pCLE) images to assess crypts, vessel architecture, and fluorescein leakage, providing an accurate assessment of mucosal healing.[32,33]

An intriguing avenue for clinical practice involves the application of AI in IBD molecular endoscopy to predict response to therapy. Iacucci et al developed AI-aided pCLE's ability to predict response to biologics, incorporating both endoscopic imaging and molecular data.[34] This study has introduced the endo-omics paradigm, where combining AI-enabled endoscopy with OMIC data—encompassing genomics, transcriptomics, and metagenomics—can shape the future of precision medicine in IBD. This example of using AI to incorporate multiple different types of data will become increasingly common in research programs.

AI-aided Capsule Endoscopy in IBD

Capsule endoscopy (CE) has become a valuable, noninvasive, and patient-friendly imaging tool for assessing disease localization and activity in patients with suspected or established Crohn's disease (CD). However, time-consuming reading and inter-observer variability limit its applicability in daily practice. Several studies have explored the role of CE imaging-enabled AI for disease diagnosis, evaluation of extent, severity, and early stricture (Supplementary Table 1). Klang et al showed that the AI algorithm identified ulcers with high accuracy. AUC for individual patient-level experiments was 0.94 to 0.99, CD-associated strictures and normal mucosa with an AUC of 0.98, and between strictures and ulcers were 0.94.[35,36] Similarly, Ferreira et al developed an AI model to detect both enteric and colonic ulcers with a sensitivity of 83% and specificity of 98% and erosions with 91% and 93%, respectively.[37] Furthermore, AI-enabled CE has the potential to predict future prognoses. Kellerman et al demonstrated a CE AI model with accuracy of 81%, with an AUC of 0.86%, in predicting the requirement for biological therapy over 6 months in CD.[38] Recently, Brodersen et al conducted a multicenter prospective study assessing pan-enteric CE analysis using the AXARO AI platform in patients with suspected CD.[39] Results showed observers achieved 92% to 96% sensitivity and 80% to 83% specificity for CD detection and 97% sensitivity and 90% to 91% specificity for IBD. AI reduced initial review time to a median of 3.2 minutes.[39] Integration of AI with CE represents enhanced diagnostic accuracy and reduced review time while providing an objective and reproducible outcome, ushering in precision medicine in CD care utilizing CE.

AI-aided Histology Interpretation for IBD Assessment

Although endoscopic remission is the primary treatment goal in IBD, histological remission is considered a new target in IBD as a potentially more comprehensive parameter for long-term prognosis prediction.[11,40] International organizations have developed and recommended several histologic scores to evaluate disease activity and remission objectively.[41,42] Nonetheless, these systems remain subjective, mainly expert-exclusive, and time-consuming.

Several AI models have been developed (Supplementary Table 2) in response to these limitations to offer an objective, accurate, reproducible, and prompt assessment of IBD histologic activity (Figure 2).[43–47] Iacucci et al developed an AI model, a simplified PICaSSO Histologic Remission Index (PHRI), based on the presence or absence of neutrophils implemented for assessing histology healing in UC.[43,47–49] The AI-assessed PHRI also demonstrated a hazard ratio of 4.64 for predicting future UC clinical flare within 1 year, potentially helping guide treatment decisions.[47]

In related work, Rymarczyk and colleagues recently proposed novel models for assessing histology disease activity in both UC and CD.[46] Using mucosal biopsy histology slides from phase II and phase III clinical trials; they developed AI frameworks based on the Global Histology Activity Score (GHAS) for CD and Geboes subgrades for UC. These models achieved accuracies ranging from 80% to 89% for GHAS in the colon, 65% to 82% for GHAS in the ileum, and 65% to 85% for Geboes scale. Automating histologic disease activity enables standardization and efficiency for incorporating histopathologic processing into clinical trials. Of equal importance,

automated and remote histologic image severity grading for CD and UC provides new possibilities for retrospective population-based disease activity assessments for conventional clinical care.

AI-aided Radiology in IBD

The use of AI in IBD radiology is growing rapidly. Computed tomography enterography and magnetic resonance enterography play pivotal roles in establishing a diagnosis of CD, following response to therapy, and quantifying disease activity.[50] Multiple groups have developed models to measure structural bowel damage in CD with performance comparable to those of experienced radiologists in less time (Supplementary Table 3).[51,52] Standard radiologic parameters modeled included bowel wall thickness, maximum bowel dilation, minimum lumen diameter, and the presence of strictures. Mahapatra et al extracted features related to shape and intensities from magnetic resonance imaging (MRI) images, merging them with AI models to segment inflammatory lesions individually in 26 MRI examinations.[53] Their model exhibited a sensitivity of over 90% and a specificity over 75% in detecting inflammation. Holland et al developed an AI model to identify IBD disease severity based on magnetic resonance enterography imaging; they achieved 100% accuracy in detecting severe cases, strongly correlating with the magnetic resonance index of activity (MaRIA) score.[54] Meng et al developed a model based on computed tomography enterography for characterizing strictures in patients with CD.[55] In the analysis of 312 bowel segments, the model achieved superior performance compared with 2 radiologists while requiring significantly less time.

Radiomics, defined as the quantification of medical image features related to prediction targets such as clinical endpoints and genomic features, have evolved to assist radiologists in clinical decision-making and improve disease severity assessment.[56] Li et al developed a nomogram based on radiomic features to distinguish CD and UC with an AUC of 0.88, significantly higher than clinical models.[57] Through radiomics disease feature extraction, Ding et al attempted to stratify CD severity in the terminal ileum using an MR examination approach with comparable results to MaRIA scores assigned by radiologists.[58] Radiomic-based nomograms are also being developed to detect loss of response to therapy and predict response to treatment.[59,60] Puylaert et al developed and validated the VIGOR score for ileocolonic CD, combining semi-automatic measurement of MRI features with radiologists' evaluation of magnetic resonance images.[61] Their score proved as accurate as conventional MRI and provided a more objective approach for disease monitoring, addressing interobserver variability.

AI Applications in Clinical Trials and Research

AI in IBD Clinical Trials

Randomized placebo-controlled trials (RCTs) are necessary but suffer from significant capital requirements, limited recruitment of underrepresented populations, and restrictive inclusion criteria. AI can help streamline the process, including improving enrollment, objective disease activity scoring, and even molecule development (Figure 1).[62] To reduce the time required for recruiting, companies are using AI-enabled endoscopic video evaluation and EHR data to automatically determine if a patient meets the screening criteria.[63] Future RCTs may not require an equal number of placebo arm subjects, as AI-generated synthetic control arms and AI-generated digital twins are showing promise in simulating non-active comparitors.[64,65] Many of the AI approaches to automate endoscopic and histologic disease severity discussed in preceding sections have the opportunity to reduce trial costs incurred by expert central readers.[23,47] AI is being used in pre-clinical research to accelerate identification of potential therapeutic molecules and anticipated drug toxicity.[66–68] Currently, an AI-discovered agent for UC, ISM5411, is in phase Ib trial.[69]

AI also introduces improved means for automating the monitoring of patient safety with constant drug surveillance embedded within EHRs. Silverman et al have developed algorithms to isolate adverse events documented in outpatient IBD clinic notes occurring while on an IBD advanced therapy.[70] These tools can be used to discover new safety signals and tailor discussions with patients around safety. Not only will such safety tools help in population-level monitoring of post-marketing medication surveillance, but all offer tools clinicians can use for individual patients to detect medication-associated adverse events. Overall, AI has the potential to impact the entire life cycle of therapeutics research, development, and safety in IBD.

AI Applications in IBD Clinical Research

AI has demonstrated the ability to produce insights into important disease outcomes using clinical data (Table 1). AI-powered models can help predict future hospitalization or outpatient corticosteroid use in IBD using administrative data in the Veterans Health Administration.[71] The same research group also developed a prediction algorithm for achievement of remission in patients on thiopurines.[72] Patients in algorithm-predicted remission had significantly fewer steroid prescriptions, hospitalizations, or surgeries. In addition, AI applications in IBD can improve the value of care provided (Figure 1). Implementation of the thiopurine

Table 1. AI Applications in IBD Research

Author, year	Study design	Technique	Population	Main findings
Waljee et al, 2017[71]	Retrospective multicenter	Clinical structured data	20,368 IBD patients	AUC 0.85 (95% CI, 0.84–0.85) predicting the combined endpoint of corticosteroid use or hospitalization.
Waljee et al, 2017[72]	Retrospective single-center	Clinical structured data and unstructured data via manual chart review	1080 IBD patients	AUC 0.79 (95% CI, 0.78–0.81) predicting disease remission in patients receiving thiopurines from structured laboratory values.
Waljee et al, 2018[80]	Prospective multicenter	Phase III clinical trial structured data	472 CD patients	AUC 0.75 (95% CI: 0.64–0.86) for prediction of corticosteroid-free endoscopic remission in CD patients receiving vedolizumab at week 52 using baseline and week 6 data. Patients algorithmicly predicted to fail only succeeded 6.7% of the time.
Miyoshi et al, 2021[81]	Retrospective multicenter	Clinical structured data and unstructured data via manual chart review	34 UC patients – training 35 UC patients – test	PPV 54% and NPV 92% predicting steroid-free clinical remission at week 22 in UC patients receiving vedolizumab.
Waljee et al, 2019[82]	Prospective multicenter	Phase III clinical trial structured data	401 CD patients	AUC of 0.78 (95% CI, 0.69-0.87) for prediction of response to ustekinumab defined by CRP $<$ 5 mg/dL after week 42, from week 8 clinical and laboratory data.
Fernandes et al, 2023[75]	Prospective multicenter	RISK cohort SRA enteroid	RISK – 243 pediatric CD patients and 43 age-matched healthy controls SRA 16 CD patients and 12 controls	Metabolic models of CD in both RISK tissue and enteroids showed that fatty acid metabolism was a common biological process.
Yang et al, 2024[76]	Retrospective multicenter	Gene Expression Omnibus Database	233 UC mucosal samples and 88 healthy controls – train and test 162 UC mucosal samples and 21 healthy controls - validation	8 signature genes were identified, including S100A8, IL-1B, CXCL1, TCN1, MMP10, GREM1, DUOX2, and SLC6A14, which exhibit mild to moderate correlation with UC patient's Mayo scores.
Romagnoni et al, 2019[77]	Retrospective multicenter	International IBD Genetics Consortium	18,227 CD patients and 34,050 controls	AUC, 0.80 classifying healthy vs CD patients based solely on their genomic information.
O'Brien et al, 2024[78]	Retrospective single-center	Clinical structured data and unstructured data via manual chart review	63 IBD patients and 118 controls	Model accurately predict disease activity quantified by the physicians' global assessment based on serum cytokine levels.

Table 1. Continued

Author, year	Study design	Technique	Population	Main findings
Verstockt et al, 2020[83]	Prospective multicenter	Clinical structured data and unstructured data via manual chart review. Genetic and transcipomics data from colonic biopsies.	31 IBD patients – train 53 IBD patients – test	Model identified 4 genes expressed in inflamed colon tissue were associated with endoscopic remission after vedolizumab but not anti-TNF factor treatment.
Cushing et al, 2019[84]	Prospective single-center	Clinical structured data and unstructured data via manual chart review. Genetic and transcipomics data from ileal surgical specimens.	65 CD patients	Model accurately separates patients with indolent Crohn's disease vs progressive disease after surgery using whole transcriptome profiles of ileal tissue.
Silverman et al, 2024[98]	Retrospective single-center	Clinical unstructured data via manual chart review	928 IBD patients	Model accurate, 88%–92%, at identifying serious adverse events after initiation of advanced therapy in outaptient IBD clinic notes.

AI, Artificial intelligence; Anti-TNF, anti-tumor necrosis factor; AUC, area under the curve; CD, Crohn's disease; CRP, c-reactive protein; IBD, inflammatory bowel disease; NPV, negative predictive value; PPV, positive predictive value; SRA, sequence read archive; UC, ulcerative colitis.

algorithm, where it replaced laboratory measurement of thiopurine metabolites, saved $75,000 per year.

There is an unmet need to understand how clinical, molecular, and microbial factors contribute to the mechanisms driving IBD, but the relationships are complex.[73,74] Studies have leveraged AI to guide basic science research as idea-generating methods (Table 1). Fernandes et al piloted computational metabolic modeling the molecular profiles of CD compared with control tissue to show that fatty acid metabolism was a common biological process in each cohort.[75] Yang et al used AI to evaluate possible new genetic signatures in UC and analyzed their correlation with patients' Mayo scores.[76] Additionally, Romagnoni et al found that AI could classify healthy patients vs patients with CD based solely on their genomic information.[77] Interestingly, AI detected almost all of the genetic variants previously identified by genome-wide association studies (GWAS) as the best predictors plus additional predictors that represent targets for future research. O'Brien et al used AI to predict disease activity quantified by the physicians global assessment based on serum cytokine levels.[78]

The decision of which medication to use and when to change therapy can be challenging. AI can identify patients early who are unlikely to achieve steroid-free endoscopic remission to different therapies, facilitating data-driven changes in medication.[79–82] In addition, Verstockt et al, using AI, identified 4 genes expressed in inflamed colon tissue whose baseline expression levels were associated with endoscopic remission after vedolizumab but not anti-tumor necrosis factor (TNF) treatment.[83] Cushing et al used AI to separate patients with indolent CD vs progressive disease after surgery using whole transcriptome profiles.[84] The model isolated 30 transcripts differentiating patients with Rutgeerts score i0 from higher scores. Notably, patients with indolent disease, i0, who were anti-TNF naïve, had lower Bcl2 mediated apoptosis. Authors suggest this might be able to be used as a marker of disease remission in anti-TNF-naïve patients. The ideal future state of AI in IBD would be models trained on multi-center multi-modal data encompassing clinical, laboratory, radiology, endoscopy, omics, dietary, and environmental data with the output being clinically actionable information such as response to therapy (Figure 3).

Ethics, Implementation, and Future Challenges for AI in IBD

Several challenges still need to be addressed prior to widespread implementation of AI in clinical practice.[85] Despite the advantages of AI discussed, interpretability has been noted as a concern.[86,87] Tools such as the Minimal Information about Clinical Artificial Intelligence Modeling (MI-CLAIM) checklist aim to guide training and test-cohort selection, development, and validation methods.[88] In addition, institutional and regional

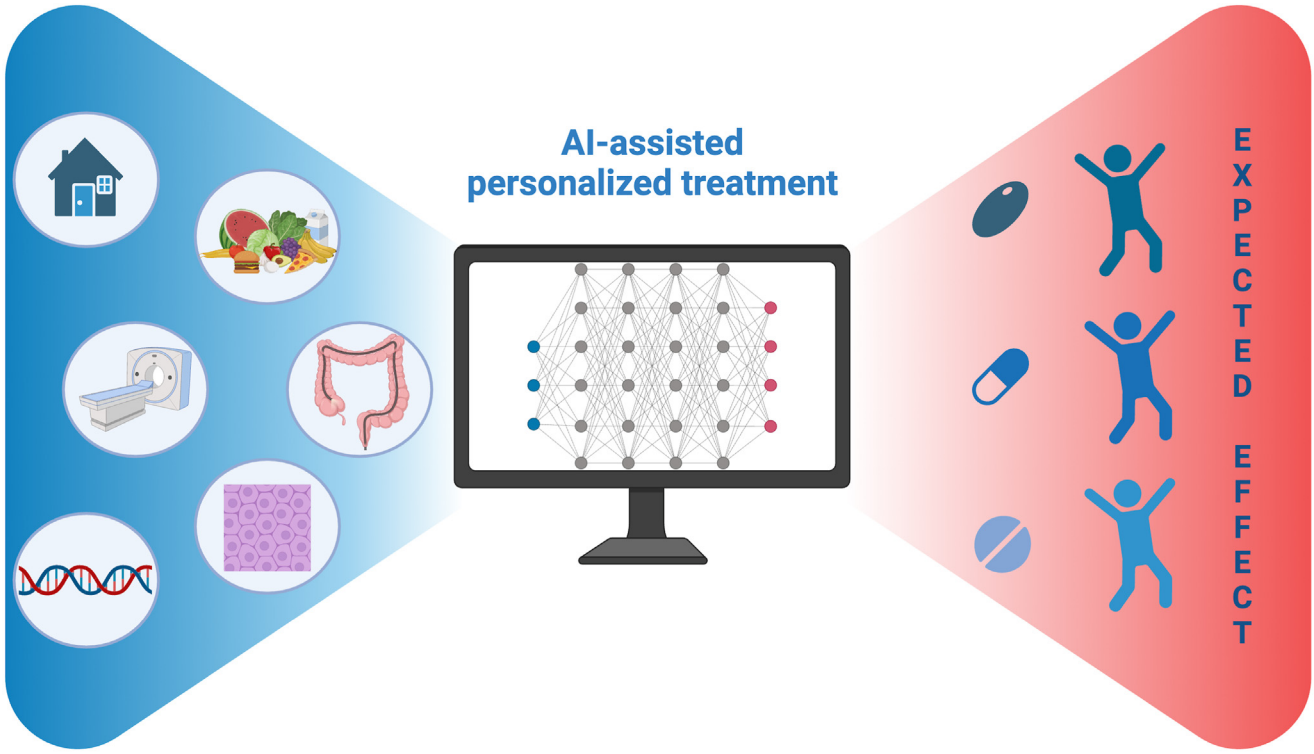

Figure 3. The ideal future-state of AI in IBD clinical research would be models trained on multi-center multi-modal data encompassing clinical, laboratory, radiology, endoscopy, omics, dietary, and environmental data with the output of models being clinically actionable information, such as response to therapy.

variations in practice and documentation affect both model performance and model interpretation of local data.[89] Furthermore, IBD suffers from data scarcity. Large de-identified multi-institution datasets are critical for useful AI model development, but changes in institutional cooperation, assurance of patient privacy, and provider education on interpreting AI results remain unanswered challenges.

Most AI efforts in IBD are in the initial research phases and have not yet gone through prospective evaluation to earn regulatory approval by national regulatory bodies.[90] AI will need to undergo RCTs themselves for implementation of clinical AI from bench to bedside. Importantly, to ensure rigor in design and consistent publication standards, protocol and reporting guidelines have been proposed. The Enhancing the Quality and Transparency of Health Research (EQUATOR) network has put forth the Standard Protocol Items: Recommendations for Interventional Trials-Artificial Intelligence (SPIRIT-AI) and Consolidated Standards of Reporting Trials-Artificial Intelligence (CONSORT-AI).[91,92]

Even after prospective evaluation, AI used in real-world clinical care may not perform as expected when exposed to new health care systems, populations, practice patterns, and types of data.[93–95] Generalizability limitations of even well-tested AI models was highlighted in the external validation of EHR vendor EPIC's proprietary sepsis detection algorithm, whose performance significantly declined in real-world use compared with the testing environment (AUC, 0.63).[96] Safe implementation of AI tools in clinical environments will demand governance for implementation best practices and surveillance strategies to monitor model performance and utility in deployment.

Finally, AI has humbled many, as it highlights unrecognized biases in our practice patterns and in the questions asked by the health care community. For example, a population health-management algorithm used to predict future health care costs as a proxy for health care needs introduced large-scale racial bias.[97] Great care and expertise producing and consuming real-world clinical data will be needed to mitigate baking bias in models. Notably, there are structural challenges in medicine that technology will be unable to solve. Despite these challenges, AI is an innovative tool with immense potential to integrate traditionally disparate data, guide research and practice, and facilitate personalized diagnostic and therapeutic approaches.

Conclusion

As AI capabilities continue to evolve, the near future holds promise for AI's widespread and practical use in real-life medical scenarios. Although significant challenges remain, the speed at which progress is being made in health care-applied AI suggests that these

methods hold significant promise for the care and research of many diseases, including IBD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.05.048.

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Conflicts of interest
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Supplementary Table 1. AI in Endoscopy for IBD

Author, year	Study design	Technique	Population	Main finding
Stidham et al, 2019[13]	Retrospective single-center	Colonoscopy	16,514 images from 3082 UC patients 1652 images from 304 UC images – testing	83% sensitivity and 96% specificity in differentiating MES 0–1 from MES >1
Ozawa et al, 2019[14]	Retrospective single-center	Colonoscopy	26,304 images from 841 UC patients – training 3981 images from 114 UC patients – testing	0.86 and 0.98 AUC in identifying MES 0 and MES 0–1, respectively
Takenaka et al, 2020[15]	Prospective single-center	Colonoscopy	40,758 images and 6885 biopsies from 2012 UC patients – training 4187 images and 4104 biopsies from 875 UC patients - testing	93.3% sensitivity, 87.8% specificity and 90.1% accuracy in identifying ER by UCEIS 92.4% sensitivity, 93.5% specificity and 92.9% accuracy in identifying HR by Geboes score Hazard ratio of 48.4, 46.4, 10.2 and 8.8 for prediction of hospitalization, colectomy, steroid use, and relapse, respectively
Bhambhvani et al, 2021[16]	Retrospective single-center	Colonoscopy	777 still images from 777 UC patients	72.4% sensitivity, 85.7% specificity, and 77.2% accuracy in identifying MES
Lo et al, 2022[17]	Retrospective single-center	Colonoscopy	1484 images from 467 UC patients	93% sensitivity, 94% specificity, and 94% accuracy in identifying MES 0 90% sensitivity, 96% specificity, and 91% accuracy in differentiating MES 0–1 from 2–3
Gottlieb et al, 2021[18]	Prospective multicenter	Colonoscopy	795 videos from 249 UC patients	95.5% and 97.04% accuracy in differentiating MES 0 from 1–3 and UCEIS 0–1 from 2–8, respectively
Sutton et al, 2022[19]	Retrospective single-center	Colonoscopy	851 UC images	79% sensitivity, 91% specificity, 87.5% accuracy in differentiating MES 0–1 from 2–3
Takenaka et al, 2022[20]	Prospective multicenter	Colonoscopy	900 biopsies from 770 UC patients	97.9% sensitivity and 94.6% specificity for prediction of HR
Byrne et al, 2023[21]	Prospective single-center	Colonoscopy	134 UC videos	96.7% sensitivity, 91.3% specificity, and 94% accuracy in differentiating MES 0–1 from 2–3
Iacucci et al, 2023[29]	Prospective multicenter	Colonoscopy	1090 videos from 283 UC patients	72% sensitivity and 87% specificity to predict ER by UCEIS and PICaSSO with WLE 79% sensitivity and 87% specificity to predict ER by UCEIS and PICaSSO with VCE
Bossuyt et al, 2020[25]	Prospective multicenter	Colonoscopy	29 UC and 6 control patients	Strong correlation of red density score with MES, UCEIS, and RHI (r 0.76, 0.74, and 0.74, respectively)

Supplementary Table 1. Continued

Author, year	Study design	Technique	Population	Main finding
Kuroki et al, 2024[24]	Prospective single-center	Colonoscopy	8853 images from 167 UC patients 7763 images from 154 patients – training 1090 images from 13 patients - testing	100% sensitivity, 39.3% specificity, and 51.4% accuracy of AI vascular-healing model in predicting 12 months-clinical relapse. Significantly higher clinical relapse rate in AI-based vascular-active group (23.9%) than AI-based vascular-healing group (3.0%).
Quènèhervè et al, 2019[32]	Retrospective multicenter	pCLE	23 CD, 27 UC, and 9 control patients	100% sensitivity and specificity in differentiating healthy subjects from IBD 92% sensitivity and 91% specificity in differentiating UC from CD
Udristoiu et al, 2021[33]	Prospective Single-center	pCLE	32 active CD, 18 quiescent CD and 4 control patients	94.6% sensitivity and 92.8% specificity in differentiating inflamed from normal mucosa in CD
Iacucci et al, 2023[34]	Prospective single-center	pCLE	29 IBD patients	85% and 80% accuracy in predicting response to biologics in CD and UC, respectively
Maeda et al, 2019[30]	Retrospective single-center	Endocytoscope	87 UC patients for training 100 UC patients for testing	74% sensitivity, 97% specificity, and 91% accuracy in predicting histologic inflammation by Geboes score
Klang et al, 2020[35]	Retrospective single-center	Capsule endoscopy	17,640 images from 49 CD patients	Accuracies ranging from 95.4% to 96.7% in detection of small-bowel ulcers in CD
Klang et al, 2021[36]	Retrospective single-center	Capsule endoscopy	27,892 images; 1942 strictures images, 14,266 normal mucosa images, and 11 684 ulcer images.	93.5% accuracy for classifying strictures vs non-strictures
Ferreira et al, 2022[37]	Retrospective multicenter	Capsule endoscopy	8085 images of CD patients	90% sensitivity and 96% specificity in detection of ulcers and erosions of the small intestine and colon
Kellerman et al, 2023[38]	Retrospective multicenter	Capsule endoscopy	101 CD patients	81% accuracy in prediction of the need for biological therapy
Brodersen et al, 2023[39]	Prospective multicenter	Capsule endoscopy	131 suspected CD patients	92%–96% sensitivity and 90%–83% specificity for CD detection and 97% sensitivity and 90%–91% specificity for IBD

AI, Artificial intelligence; AUC, area under curve; CD, Crohn's disease; ER, endoscopic remission; HR, histological remission; IBD, inflammatory bowel disease; MES, Mayo endoscopic subscore; pCLE, probe-based confocal laser endomicroscopy; PICaSSO, Paddington International Virtual Chromoendoscopy Score; RHI, Robarts Histopathology Index; UC, ulcerative colitis; UCEIS, ulcerative colitis endoscopic index of severity.

Supplementary Table 2. AI in Histology for IBD

Author, year	Study design	Technique	Population	Main findings
Gui et al, 2022[43]	Prospective multi-center	Histology	614 biopsies from 307 UC patients	78% sensitivity, 91.7% specificity, and 86% accuracy in predicting HR by PHRI
Vande Casteele et al, 2022[44]	Retrospective single-center	Histology	88 UC patients	86.4% sensitivity in identifying eosinophils
Najdawi et al, 2023[45]	Retrospective single-center	Histology	512 WSI from 334 UC patients for training 308 WSI from 243 patients for testing	97% accuracy in predicting HR by NHI
Rymarczyk et al, 2023[46]	Retrospective multi-center	Histology	2935 biopsies from 302 CD patients 3496 biopsies from 887 UC patients	80%–89% and 65%–85% accuracy in predicting GHAS for CD and Geboes for UC, respectively
Iacucci et al, 2023[47]	Prospective multi-center	Histology	535 biopsies from 273 UC patients	94% sensitivity, 76% specificity, and 80% accuracy in distinguishing HR vs activity by RHI 89% sensitivity, 79% specificity, and 81% accuracy in distinguishing HR vs activity by NHI 89% sensitivity, 85% specificity, and 90% accuracy in distinguishing HR vs activity by PHRI Hazard ratio of 4.64 in predict disease flare-up by HR/activity by PHRI

AI, Artificial intelligence; CD, Crohn's disease; GHAS, Global Histological Activity Score; IBD, inflammatory bowel disease; HR, histological remission; NHI, Nancy Histological Index; PHRI, PICaSSO Histological Remission Index; RHI, Robarts Histopathology Index; UC, ulcerative colitis; WSI, whole-slide imaging.

Supplementary Table 3. AI in Radiology for IBD

Author, year	Study design	Technique	Population	Main findings
Stidham et al, 2020[51]	Retrospective single-center	CT enterography	138 CD patients	Similar correlation between radiologists and model for inflammatory parameters such as BWT-max (r = 0.72, 0.70), DIL-max (r = 0.81, 0.75), and LUM-min (r = 0.43,0.38) Model was 88% accurate in detection of strictures
Lamash et al, 2019[52]	Retrospective single-center	MR enterography	23 pediatric CD patients	DSCs of 75% ± 18%, 81% ± 8%, and 97% ± 2% for the lumen, wall, and background Median value of relative contrast enhancement ($P = .0033$) could differentiate active and nonactive disease segments
Mahapatra et al, 2016[53]	Retrospective multicenter	MR enterography	70 CD patients	Sensitivity of over 90% and a specificity of over 75% in detecting inflammation
Holland et al, 2019[54]	Retrospective single-center	MR enterography	170 CD patients	F1 score of 0.83, with 100% accuracy in detecting severe cases, strongly correlating with the MaRIA score
Meng et al, 2022[55]	Retrospective multicenter	CT enterography	235 CD patients	Statistically superior model performance compared with radiologists ($P < .05$) at distinguishing mild vs severe bowel fibrosis
Li et al, 2021[57]	Retrospective single-center	CT enterography	99 CD and 66 UC patients	CD radiomics features, achieving an AUC of 0.88, acting as new tool for radiologists to differentiate between CD and UC
Ding et al, 2022[58]	Retrospective multicenter	MR enterography	121 CD patients	Radiomics model was developed with 6 reproducible features (ICC = 0.93–0.96) and equivalent to expert radiologist assigning a MaRIA score
Puylaert et al, 2018	Retrospective – train Prospective – test single-center	MR enterography	27 CD patients – train 106 CD patients – test	Semi automatic VIGOR score comparable to the performance of the CDEIS score with diagnostic accuracy of 81%.

AI, Artificial intelligence; AUC, area under the curve; BWT-max, maximum bowel wall thickness; CD, Crohn's disease; CDEIS score, Crohn's disease endoscopic index of severity score; DIL-max, maximum bowel dilation; DSC, dice similarity coefficeint; ICC, intra-class corelation coefficient; LUM-min, minimum lumen diameter; MaRIA score, magnetic resonance index of activity score; VIGOR score, virtual gastrointestinal tract score.

Culturally Sensitive and Inclusive IBD Care

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As the prevalence of inflammatory bowel disease (IBD) increases within historically disadvantaged communities, it is imperative to better understand how intersectionality—defined as the complex, cumulative way in which the effects of multiple forms of discrimination (such as racism, sexism, and classism)—intersects and social determinants of health influence the patient's experiences within the medical system when navigating their disease. Culturally sensitive care is characterized by the ability to deliver patient-centered care that recognizes how the intersectionality of an individual's identities impacts their disease journey. An intentional consideration and sensitivity to this impact play important roles in providing an inclusive and welcoming space for historically disadvantaged individuals living with IBD and will help address health inequity in IBD. Cultural competence implies mastery of care that understands and respects values and beliefs across cultures, while cultural humility involves recognizing the complexity of cultural identity and engaging in an ongoing learning process from individual patient experiences. Heightening our patient care goals from cultural competence to cultural sensitivity allows healthcare professionals and the systems in which they practice to lead with cultural humility as they adopt a more inclusive and humble perspective when caring for patient groups with a diverse array of identities and cultures and to avoid maintaining the status quo of implicit and explicit biases that impede the delivery of quality IBD care. In this article, we review the literature on IBD care in historically disadvantaged communities, address culturally sensitive care, and propose a framework to incorporating cultural humility in IBD practices and research.

Keywords: Diversity; Equity; Inclusion; Inflammatory Bowel Disease; IBD; Crohn's Disease; Ulcerative Colitis; Race; Ethnicity; Racism; Social Determinants Of Health; Sexual Minorities; Gender Minorities; LGBTQ+; Artificial Intelligence; AI.

Culturally sensitive care is the delivery of patient-centered care that acknowledges and values the intricate interplay of various factors such as race, ethnicity, nationality, gender, sexual orientation, and heritage, all of which influence an individual's health.[1] As the worldwide incidence of inflammatory bowel diseases (IBDs) continues to increase, the epidemiology of IBD is drastically shifting from being a disease that predominantly impacts individuals of Northern European heritage to a more global disease with sharp rises in incidence in other developed and developing countries.[2,3] With the increasing diversity of populations with IBD, gastroenterologists and other healthcare providers need to be cognizant of the impact and influence of an individual's intersectionality of identities on their experience living with a chronic illness such as IBD. Intersectionality refers to the interconnected nature of social categories of identities that acknowledges how individuals can experience multiple forms of oppression or privilege simultaneously due to the overlap of their various identities.[4] Historically disadvantaged communities—including Black, Hispanic/Latinx, American Indian and Alaska Native, Asian American and Pacific Islander, and other persons of color; members of religious minority groups; LGBTQ+ persons; persons with disabilities; persons who live in rural areas; and persons otherwise adversely affected by persistent poverty or inequality[5]—fare worse with IBD, as evidenced by observed health disparities that will be referenced in this review. For IBD providers to provide culturally sensitive care and respond to the diverse needs of their patients, they need to acknowledge, understand, and address the intersectionality of identities and their impact on a patient's IBD-related outcomes.

Given the unique challenges that various communities referenced previously may endure in their IBD care, a "one-size-fits-all" approach is unlikely to promote optimal outcomes when applied to diverse populations. Understanding this challenge, and honoring the value of intersectionality, this review will focus on the importance of culturally sensitive care for persons from racial and ethnic minority groups and LGBTQ+ populations. In this review, we detail the current literature on the impact of social and behavioral determinants of health on IBD outcomes, closely examine the deleterious effects of

Abbreviations used in this paper: **AI, artificial intelligence; CRC, colorectal cancer; GAHT, gender-affirming hormonal therapy; IBD, inflammatory bowel disease; SDoH, social determinants of health; TGD, transgender or gender diverse; VTE, venous thromboembolism.**

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specific sociocultural barriers to care on the health of the LGBTQ+ community living with IBD, and finally and most critically, we propose creative solutions for implementing culturally sensitive care for our ever-growing racially, ethnically, and gender-diverse communities of patients living with IBD.

Social and Behavioral Determinants of Health

A crucial aspect of providing culturally sensitive and inclusive care involves recognizing the significant influence that social and behavioral determinants of health have on health equity. Social determinants of health (SDoH) are defined as the complex, integrated, and overlapping social structures and economic systems that may contribute to health inequities.[6] Behavioral determinants of health include health-promoting and health-related risk behavior shaped by SDoH.[6] Typically, interventions to close the chasm of health disparities are misguided, focusing most heavily on an individual's behaviors, rather than addressing the proximate social determinants of that behavior. Historically disadvantaged populations are disproportionately impacted by systemic racism, poorer access to educational opportunities, housing instability, neighborhood zoning segregation, inadequate transportation, poor Internet connectivity, and violent crimes.[6] The Centers for Disease Control and Prevention's focus of their Healthy People 2030 initiative, which sets data-driven national objectives to improve health and well-being over the next decade, prioritizes addressing SDoH, along with health literacy and equity, as 1 of the 3 key components to center its efforts.[6]

Additionally, it is important to consider sociocultural differences in the delivery of care among historically disadvantaged groups, and to regard these differences as additional SDoH due to their impact on physician-patient relationships and subsequently health outcomes.[7] For instance, prior studies show that patients from culturally or linguistically diverse backgrounds face additional barriers compared with the native-born population, such as language, legal obstacles (such as with immigration status), and differences in healthcare-seeking beliefs and behaviors.[8] These barriers often result in lower access to healthcare services among disadvantaged populations and can impact the delivery of quality care. Moreover, language discordance between healthcare providers and patients can lead to mistrust, dissatisfaction, decreased adherence to recommended plans, and ultimately poor health outcomes.[9,10] Therefore, as it is estimated by 2050 that 50% of the U.S. population will be members of historically disadvantaged racial and ethnic populations (25% Hispanic, 14.4% African American, and 8.6% Asian),[11] developing and implementing an evidence-based approach to prioritizing resource allocation and delivering culturally tailored care to these populations is of paramount importance.

Racial and Ethnic Historically Disadvantaged Communities with IBD

Impact of Racial and Ethnic SDoH on IBD Outcomes

Studies have demonstrated how disparities in process and outcome measures exist across the continuum of care for patients with IBD from racial and ethnic historically disadvantaged communities with IBD. In a review by Anyane-Yeboa et al,[12] the authors grouped SDoH in IBD into upstream, midstream, and downstream determinants that ultimately impact patients with IBD. Examples of upstream determinants include systemic racism, socioeconomic status, gender inequities, and immigration status (Figure 1). It is critical to affirm that it is racism—defined as organized systems within societies that cause avoidable and unfair inequalities in power, resources, capacities and opportunities across racial or ethnic groups[13]—and not race, that is the determinant that impacts the downstream SDoH and disparate IBD health outcomes. Race is a social, not biologic or scientific, construct borne out of a need to systematically disenfranchise, oppress, and deny privilege and power to particular groups based on the social perception of their physical characteristics.[13] Ethnicity is a social construct that defines a group of people who identify with each other on perceived attributes such as ancestry, nation of origin, traditions, language, history, or religion, such as Hispanic ethnicity. Midstream determinants are direct results of these upstream determinants and include educational attainment, employment, housing safety and quality, food and nutrition security, environmental toxicity, access to care, and psychosocial stressors.[12] Delayed diagnoses, worse disease severity, increased healthcare utilization—including emergency room visits and hospitalizations, increased need for surgery, greater fractionation of care delivery, and increased morbidity, disability, and mortality[14–19]—are all downstream consequences stemming from upstream and midstream SDoH. These disparities are especially troubling given the increasing global incidence of IBD impacting people of diverse races, ethnicities, and sexual and gender identities.[20] Therefore, systemic interventions to deliver quality care more equitably in IBD is critical to reduce morbidity and mortality associated with IBD care.

A study from South Florida examined the cumulative social barriers on IBD care among a diverse community.[21] They defined social barriers as different SDoH including nativity (U.S. born vs foreign born), housing insecurity, highest level of education obtained, and financial strain.[21] They summed up these social barriers to determine the cumulative social barriers and found that immigrant, Hispanic, and Black individuals had significantly greater social barriers (such as financial and food insecurity) than did non-Hispanic White patients with IBD.[21] Furthermore, cumulative social barriers were associated with greater disease activity among patients with ulcerative colitis, highlighting the impact SDoH have

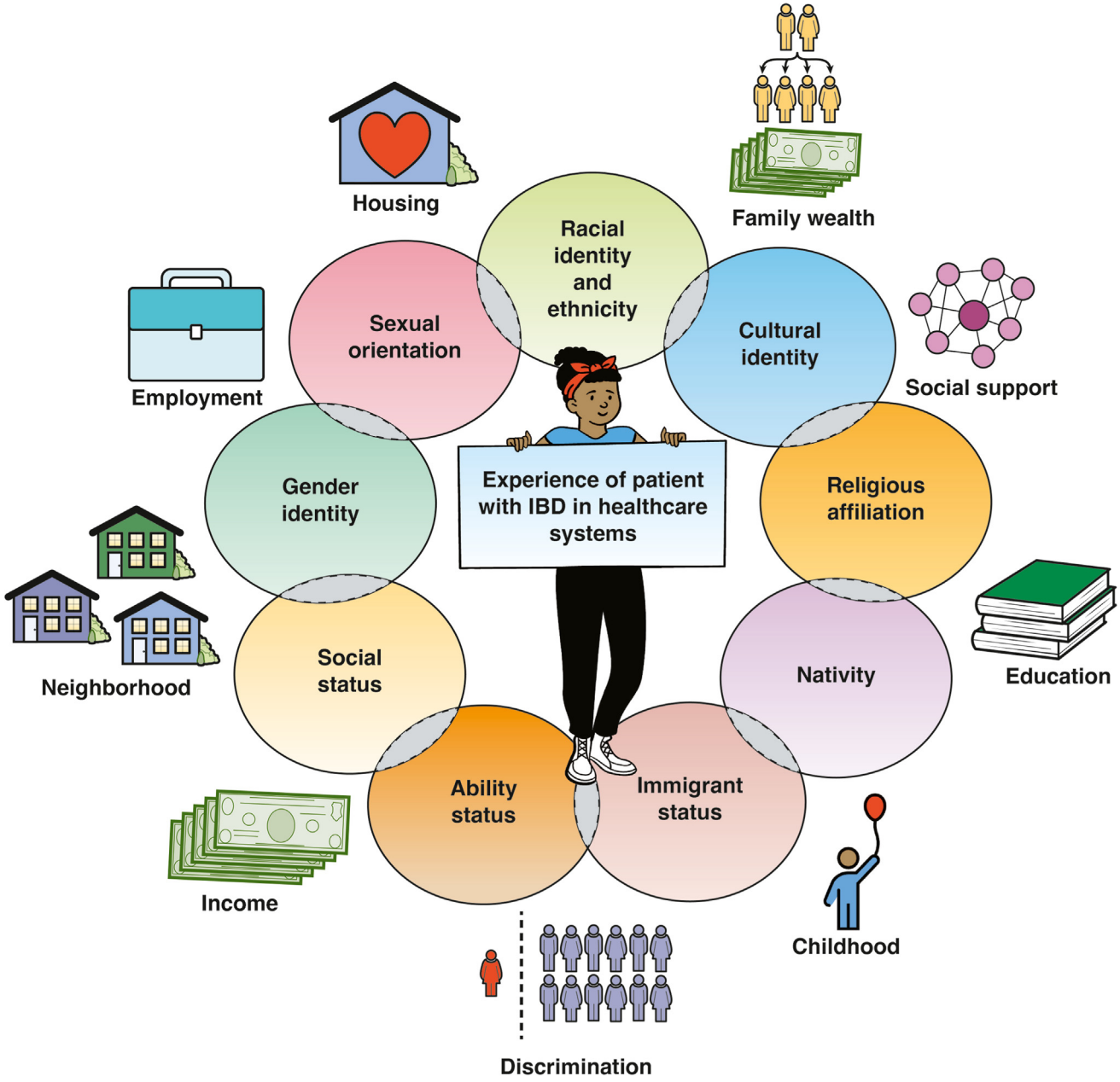


Figure 1. Relationship between intersectionality and SDoH in IBD. The interplay between intersectional identities and social determinants of health is critical—understanding the ways in which an individual's multiple minoritized identities shape their interactions with the healthcare system allows for greater appreciation of how social determinants of health impact the quality of care they receive, and the disparate outcomes that result from belonging to many historically disadvantaged groups simultaneously.

on downstream health outcomes in IBD in historically disadvantaged communities. Multiple other studies have similarly identified worse outcomes in socially vulnerable communities with IBD, including lower quality-of-life scores, lower rates of screening for depression and anxiety, and higher rates of corticosteroid use.[17,22,23]

Financial Burden and Social Support

Financial toxicity, defined as financial hardship due to medical bills, personal and health-related financial distress, and cost-related medical nonadherence, has also been observed among historically disadvantaged patients with IBD. Using the National Health Interview Survey 2015, Nguyen et al[24] estimated the prevalence of food insecurity and/or lack of social support among adult patients with IBD and evaluated associations with financial toxicity and emergency department use. The prevalence of financial toxicity was significantly higher in patients with lack of social support. Fifty-three percent of patients reported lack of social support, but rates were higher in marginalized racial and ethnic groups—Black (70%) and Hispanic (83%) patients were more likely to lack adequate social support compared with non-Hispanic White (47%) and Asian (51%) patients.[24]

Similarly, an online survey published in 2023 looking at racial and ethnic disparities in persons with IBD found that compared with their non-Hispanic White counterparts, Black, Indigenous, and people of color and Hispanic individuals reported lower rates of financial stability, lower mean health-related quality of life, more negative impact on employment, and more difficulty finding social/emotional support for IBD.[22] Another study using the National Health Interview Survey, exploring financial hardships and their impact on cost-related medication nonadherence in patients with IBD, observed that the burden of financial toxicity was not significantly impacted by race or ehtnicity.[25] Their analysis linked the burden of financial toxicity to lower education, lower family income, and insurance status.[25] Such SDoH might represent better predictors of financial toxicity and burden than race or ethnicity.

Furthermore, indirect costs among patients with IBD are quite substantive and higher than in patients without IBD.[26] Those indirect costs include, but are not limited to, absenteeism from work, reduced work productivity, premature retirement, and long-term disability. In a study from Canada, the estimated economic burden of IBD was estimated at $1.29 billion CAD in 2018.[26] They do not explore the impact of race, ethnicity or sexual orientation and gender identity on indirect cost in IBD. These indirect costs are found in the care of IBD patients and can have compounding effects if additional SDoH barriers exist, which is the case for underrepresented communities.

Disparities in Preventive Care and Healthcare Maintenance

Despite healthcare maintenance being a critical part of comprehensive care in patients with IBD, rates of preventive care are lower in this cohort of patients compared with the general population.[27] Unfortunately, racial and ethnic disparities in IBD also extend into this category of care.

In a 2023 retrospective cohort of 2453 patients with IBD, White patients were significantly more likely to be immunized against pneumococcal pneumonia, varicella zoster, and hepatitis B than were Black patients and those residing in underserved geographical areas.[28]

Additionally, it has been widely observed that racial and ethnic health disparities exist across the colorectal cancer (CRC) care continuum from screening to mortality. In the general population, Hispanic persons have the lowest screening rates, and Native American/Pacific Islanders and Black/African American individuals have the highest incidence and mortality rates from CRC.[29] However, data on CRC rates in historically disadvantaged groups with IBD are sparse and conflicting. A 2011 retrospective cohort study looked at rates of CRC in Black/African American patients with ulcerative colitis in a Veterans Affairs population and found no statistically significant difference in rates between Black/African American patients and White cohorts.[30] The authors cited that health access could be the mitigating factor attributing to lack of disparity.[30] Conversely, a retrospective multicenter cohort study in 2021 looked at 408 patients with ulcerative colitis and low-grade dysplasia and found that more patients from a Black or Asian background progressed to CRC compared with their White Caucasian counterparts despite having surveillance follow-up.[31] Additionally, those categorized as Black or Asian were more likely to have moderate-severe inflammatory activity on colonic biopsy within the 5 preceding years.[31] Further research to better understand these inconsistent trends of CRC incidence and morbidity in minority populations in IBD is needed.

Additionally, the PIANO (Pregnant in Inflammatory Bowel Disease and Neonatal Outcomes)[32] registry explored the impact of race and ethnicity on postpartum healthcare maintenance in women with IBD, showing that Black/African American women had lower rates of cervical cancer screening compared with White women. Additionally, women with a high school education and lower-income households had lower rates of hepatitis B and influenza immunization.[33]

Lack of Representation in IBD Research

Adequate representation of historically disadvantaged groups in clinical trials also contributes to disparate health and healthcare outcomes. Studies show that clinical trials spanning all areas of medicine, including IBD, lack representation of marginalized racially, ethnically, and gender-diverse groups. In a systematic review on representation of diverse groups in IBD randomized controlled trials, Pathiyil et al[34] showed that individuals least represented belong to racial and ethnic minority populations (85.3% White, 7.8% Asian, 2.0% Black, 0.2% Pacific Islander, and 4.6% other), gender-diverse individuals (none of the trials reported beyond the gender binary of male or female), elderly individuals (>65 years of age), and younger individuals (<18 years of age). Similarly, in a 2021 study looking at 55 publications detailing phase 2, phase 3, and open-label long-term extension trials of Food and Drug Administration–approved therapies in IBD, only 32 (58.2%) and 10 (19.6%) trials detailed race and ethnicity demographics, respectively; in these studies, 86.1% of the included subjects were White.

There are several factors that lead to inadequate representation of persons from racial and ethnic minority groups in clinical trials.[35] Importantly, physicians appear to be less likely to refer members of historically disadvantaged racial and ethnic communities into clinical trials.[36] Limited access to trial centers, prohibitive exclusion criteria, insufficient education about what trials entail, fear, and mistrust of medical experimentation are also commonly cited factors that limit racial and ethnic clinical trial participant diversity.[36] Additionally, from a logistics standpoint, trial designs often require multiple visits

and/or sample, endoscopic endpoints, which are difficult to commit to due to less flexible schedules among historically disadvantaged racial and ethnic communities.

Finally, and incredibly timely, mention of the increasing employment of artificial intelligence (AI) and machine learning in gastroenterology and hepatology is warranted. Despite the incredible opportunity that AI/machine learning presents for advancement in the field, Uche-Anya et al[37] provided a comprehensive understanding of how this technology may inadvertently further health disparities and inequities in clinical decision making and healthcare delivery, including clinical research.[37]

Chen et al[38] highlighted 5 vulnerable steps of healthcare AI-based systems that may work to further health inequity—problem selection, data collection, variable selection, algorithm development, and postdeployment considerations. Specific to IBD, Uche-Anya et al[37] cited a study of a cohort of over 20,000 patients with IBD from the Veterans Health Administration to create a model and algorithm that could serve to better tailor individual IBD treatment, improve patient outcomes, and reduce healthcare costs. However, the cohort used to create the model was 93% male, and included race as a predictor, despite the cohort comprising 70% White, 8% Black, 1.7% other, and 19% unknown race.[37,39] Such a mechanism to create a model that skews so heavily toward a specific population (White men) is biased and has the potential to broaden inequities seen in IBD care and management. Thankfully, the challenge to counteract such inherent biases from being reproduced as gastroenterology and hepatology more readily utilize AI-based systems is being acknowledged, and there exist formal ways to begin to mitigate the vulnerable steps in the pathway when creating AI-based systems.

LGBTQ+ Communities with IBD

Understanding the Impact of IBD in the LGBTQ+ Community

Approximately 7% of the U.S. population currently identifies as LGBTQ+ (Table 1). The prevalence of LGBTQ+ identity is even higher among adolescents and young adults, with some surveys suggesting that 1 out of 5 people under 25 years of age identifies as queer.[41] While persons with LGBTQ+ identities do not appear

Table 1. Glossary of Terms for Gender and Sexual Minority Groups

Term	Description
Cisgender	A term for people whose gender identity aligns with the gender that is socially expected based on their sex assigned at birth.
Gender diverse	A term for people with gender identities that are not constrained by binary concepts of gender (ie, man/woman).
Gender expression	Ways in which people communicate femininity, masculinity, androgyny, or other aspects of gender, often through speech, behavior, grooming, or clothing. All people make choices that express their gender.
Gender identity	A person's internal sense of being a girl/woman, a boy/man, a combination of girl/woman and boy/man, or something else (including a sense of having no gender). All people have a gender identity.
Gender minority	A broad term for the diverse group of people who experience incongruence between their gender identity and what is socially expected of them based on sex assigned at birth. This includes transgender and gender-diverse people.
Gender nonbinary	A term some people use to identify as a gender outside of the binary concept of gender. A person may identify as a combination of girl/woman and boy/man, as something else, or as having no gender. It is related to the term *gender nonconforming*.
Gender nonconforming	A term some people use to identify as a gender outside of the binary concept of gender or to describe gender expression that is incongruent with what is socially expected based on their sex assigned at birth or gender identity. It is related to the term *gender nonbinary*.
Queer	Historically a derogatory term, *queer* has been embraced by the LGBTQ communities. *Queer* can be used as an umbrella term for all sexual and gender minority people or more narrowly to represent individuals who identify outside of other categories or labels of sexual and gender identity.
Sex assigned at birth	Usually male or female, based on a medica provider's assessment of an infant's phenotypic presentation (ie, genitals). It is distinct from gender identity.
Sex	A categorization of male, female, or intersex based on biological sex characteristics (chromosomes, gonads, sex hormones, and/or genitals). Often used synonymously with *sex assigned at birth*.
Transgender man	A person who identifies as male but whose sex assigned at birth was female.
Transgender woman	A person who identifies as female but whose sex assigned at birth was male.

Table adapted with permission from Velez et al.[40]

to be at an increased risk of developing IBD, it is invariable that gastroenterologists and their care teams will have LGBTQ+ identifying people as patients.[40,42] It is important that healthcare professionals be cognizant of how identifying as LGBTQ+ may shape the experience of living with IBD and its medical and surgical management, as well as the impact that living with IBD has on the quality and richness of life for those with LGBTQ+ identities.[43]

Similarly, 0.6% of U.S. residents identify as being transgender or nonbinary, and the rate of being trans or nonbinary is 2–3 times as high among people under 25 years of age.[44] The experience of being transgender or gender diverse (TGD) is not monolithic. Some TGD people may partake in a social transition where they adopt mannerisms, behaviors, and visual cues to indicate their gender identity being different than that usually associated with their sex assigned at birth. Some, but not all, may pursue gender-affirming medical therapies and surgical interventions to induce or create the physical characteristics more typical of the sex with which they more strongly identify, or remove or attenuate physical characteristics that are associated with their birth sex. A description of the social, medical, and surgical components of gender affirming care is displayed in Figure 2.

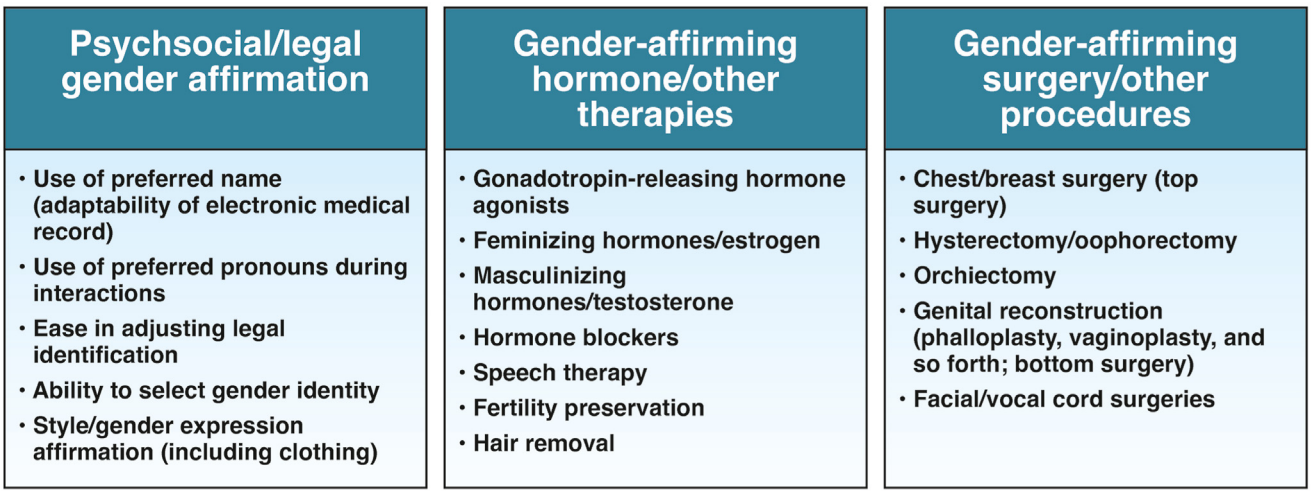
Our knowledge about the epidemiology, pathophysiology, and natural history of IBD in LGBTQ+ people is limited by the lack of focused research on this population.[43] Most IBD clinics do not consistently or routinely capture information about their patients' sexual orientation and gender identity, thereby hindering the use of this clinical data for research.[45]

There are several aspects particular to being LGBTQ+ identified that could negatively influence the health-related quality of life, including among those living with IBD.[46] In addition to the challenges typically faced by historically disadvantaged communities, LGBTQ+ people are also more likely to have experienced emotional or physical trauma compared with their straight and/or cisgender counterparts.[40] The LGBTQ+ community is a historically disadvantaged group, and is more likely than non-LGBTQ+ people to have faced discrimination that imposes challenges on one's ability to find happiness, stability, and economic success.[42] According to the minority stress model, minoritized groups experience stress stemming from experiences of stigma and discrimination, posing them at increased risk for many negative physical and mental health outcomes.[47] These life stressors and traumas lead to more susceptibility to psychological distress and adverse mental health outcomes, increased reliance on maladaptive coping mechanisms, and visceral hyperresponsiveness.[45] While the minority stress model has been used to understand and explain subjective and objective adverse healthcare outcomes in general, it has not been specifically evaluated in IBD. In the context of IBD, this may promote an increased symptom burden independent of inflammation, and higher rates of disease related disability.[48]

Special Considerations in the Care of LGBTQ+ Patients with IBD

Fear of Discrimination and Mistreatment in the Healthcare Environment

In a national, probability-based telephone survey of U.S. adults from 2017, around 57% of LGBTQ+ individuals have reported a negative experience in a healthcare setting due to their LGBTQ+ identity, and 22% have avoided or deferred medically necessary care because of previous or anticipated homophobia or transphobia in the healthcare systems.[49] Especially in a time in which discriminatory legislation targeting transgender or visibly gender-nonconforming individuals is increasing, it is critical that LGBTQ+ patients living with



Graphic adapted from Newman et al.[48]

Figure 2. Psychosocial, legal, medical, and surgical domains of gender-affirming care. This highlights the 3 main domains to gender affirmation.

IBD have a trustworthy healthcare provider respectful to their societal challenges as sexual and gender minorities.[50] There are no studies that evaluate the impact of fear of discrimination and mistreatment of LGBTQ+ individuals on IBD outcomes. Funding research to see whether similar trends of delaying care secondary to anticipated discrimination experienced by non-IBD LGBTQ+ patients exist in LGBTQ+ patients with IBD would help inform more inclusive, culturally sensitive care delivered to this population.

Sexual Health and Fertility of LGBTQ+ People With IBD

Sexual health, defined by the World Health Organization "requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence,"[51] is known to be negatively impacted in a high proportion of all people with IBD.[52] Sexual health in patients with IBD has not been studied in sexual and gender minority female-identifying, transgender, or gender-nonconforming individuals. There have been several studies that have qualitatively assessed the impact of IBD on the sexual health of gay men and on its impact on intimacy.[52] Gay men have reported concerns about body image, an inability to achieve sexual pleasure, and having to limit or change their sexual activities due to the impact of disease.[53] This would be of particular concern in people whose IBD has directly affected the function of their sexual organs, such as in perianal fistulizing disease affecting the anus or vagina, or in which surgical management has had impact on body integrity, such as in extensive abdominal scarring or stoma formation). It is important to understand that these concerns are not unique to sexual or gender minority populations.

Another important issue that is often underappreciated by clinicians is fertility and fecundity in sexual and gender minority populations.[42] It should not be presumed that women and men from sexual and gender minority populations are uninterested in having children and/or families, and therefore current and potential family planning should remain a topic of conversation between IBD clinicians and their sexual and gender minority patients.[42] Physicians should have a patient-centered informed decision-making conversations about the use of teratogenic medications in any individual with ovaries and a uterus and is of reproductive age, including transgender men.

Understanding the Impact of Gender-Affirming Hormonal Therapy in IBD

Approximately 80% of trans people are either using gender-affirming hormonal therapy (GAHT), or are interested in starting or restarting hormonal therapy.[54] The advantages are not merely cosmetic[55]—GAHT has been associated with improvements in body image, social functioning, lessened anxiety and depression, and improved quality of life.[56] At the same time, GAHT has systemic effects beyond its effects on body morphology and psychological well-being and may impact the natural history of chronic diseases like IBD. Based on studies in cisgender individuals (primarily cisgender women using postmenopausal hormones and oral contraceptives), the impact of estrogens on the incidence, natural history, and symptom burden in IBD is equivocal.[57] Greater understanding of the impact of GAHT use in IBD populations is needed in order to provide more holistic care to this specific population.

One area in which there may be heightened concern is regarding the impact of GAHT on venous thromboembolism (VTE) risk.[58] Feminizing GAHT has been associated with a 3–5 times increased risk of VTE, though this is primarily seen in persons using oral estrogen formulations, and less with subcutaneous, sublingual, and transdermal delivery.[59,60] IBD is also a prothrombotic disease, especially when in a flare requiring hospitalization.[61] Therefore, there may be scenarios in which an IBD clinician might consider recommending temporary or indefinite discontinuation of GAHT to mitigate VTE risk in someone who is in a state of increased risk or who has developed VTE.[62] It is critical that IBD clinicians be highly mindful of and sensitive to the negative psychological consequences of GAHT discontinuation. In these situations, a multidisciplinary approach that includes consultation with and guidance from a gender medicine specialist when available, and a mental health professional, to discuss with the patient the risks and treatment goals is crucial.

Surgical Considerations in Transgender Persons With IBD

IBD is a disease that directly involves the rectum and perineum. It can potentially affect the ability of a patient to undergo gender affirming surgery, or it can affect the function and appearance of gender-affirming surgeries that have been previously undertaken. For trans women, performance of a vaginoplasty requires dissecting tissue adjacent to the rectal wall to create a space for a neovagina, generally created out of penile tissue.[63] This may be contraindicated in the presence of Crohn's disease–related full thickness inflammation or extensive perirectal scarring. However, in a patient with ulcerative colitis and rectal involvement, a vaginoplasty may still be feasible. In patients who do not have adequate penile tissue to achieve satisfactory vaginal depth, vaginoplasty has traditionally been performed using a sigmoid graft to provide additional depth. A sigmoid vaginoplasty would be contraindicated in persons with a history of sigmoid involvement of their IBD, though there are no case reports of either incident or recurrent IBD in trans women who have undergone sigmoid vaginoplasty. More

commonly today, harvested peritoneal tissue is used to provide neovaginal depth, obviating the need for a sigmoid resection. Multidisciplinary planning involving an IBD specialist, IBD radiologist, colorectal surgeon, and a gender-affirming surgeon would be critical before undertaking this type of operation, with a focus on a patient's risk tolerance and goals of care.[64]

Other Considerations For TGD Patients with IBD

Recently in the United States, there has been a proliferation of discriminatory legislation targeting the trans community that limits their ability to access public bathroom facilities that are consistent with their lived gender.[50] As urgency and incontinence are common and debilitating symptoms of active IBD, especially for those with rectal involvement, uncertainty around reliable toilet access to mitigate these unpredictable symptoms can deleteriously impact their ability to fully participate in their professional and personal lives.[65] Consequently, trans people with IBD who experience urgency may be compelled to severely restrict their social activity. IBD advocacy organizations maintain lists of publicly accessible washrooms to help patients with IBD navigate in public spaces,[66] but this is unfortunately an insufficient remedy in the face of government legislation that poses limits on TGD individuals from access to bathroom facilities consistent with their lived gender. Furthermore, it is important to note that TGD persons of color experience multiple levels of marginalization (ie, racism and transphobia) in society, including healthcare systems.[67] There is a critical need to develop targeted strategies including antidiscrimination campaigns to promote the safety and health of TGD persons of color.[67]

Many trans people may also experience unease when having to expose their perineum and genitals when their genital morphology is incongruent with their gender identity. As the care of IBD frequently necessitates examination of the rectum and perineum, sensitivity and reassurance that their sexual organs will remain draped while performing a perineal and/or rectal examination may have demonstrable impact on improving the patient-physician partnership. The same principles of draping and avoiding unnecessary intimate area exposure applies as well to the performance of endoscopy.

Intersectionality of Identities and Access to Healthcare

The term *intersectionality* was first introduced by Kimberlé Crenshaw, an American civil rights activist and attorney, in 1989 to address the experiences and marginalization of Black women with regard to antidiscrimination, feminist, and antiracist theories.[68] In her work, Crenshaw described the marginalization of Black women through systems that historically were discriminatory based on race or sex.[69,70] Intersectionality was further expanded by several researchers and scholars to apply to a wide range of social identities, power dynamics, legal systems, and other structures, including healthcare systems.[71]

The main concept behind the intersectionality theory is the concept of understanding multiple identities, such as race, ethnicity, gender identities, sexual orientation, and living with IBD, in relation to each other and to the different social systems of power where these identities exist.[4] Understanding and unpacking these intersectionalities helps address and advance health equity and justice.[4] Therefore, in order to deliver culturally sensitive care in IBD, healthcare providers must understand the impact of intersectionality on healthcare outcomes. For example, a Black transgender woman with IBD would likely have multiple negative upstream SDoH that may impede her ability to experience quality healthcare and a positive relationship with the healthcare system at a disproportionate degree compared with a Black cisgender straight woman. This example highlights the compounding challenges of racism, homophobia, and transphobia for people with intersectional identities. We recognize that there have been no publications that have systematically explored the impact of intersectionality on SDoH and access to healthcare in IBD. Future work should focus on targeted interventions in IBD care that address intersectionality, SDoH, and cultural sensitivity in IBD care.

Achieving Cultural Sensitivity and Cultural Humility Rather Than Cultural Competence in IBD Care

While many publications focus on highlighting and identifying disparities in SDoH and their impact on IBD in historically disadvantaged populations, Anyane-Yeboa et al[12] examined the impact of SDoH on IBD care with a focus on solutions. The study proposed that a multilevel approach involving medical education, clinical care and research, community engagement, and hospital systems, industry, and policy may be most effective to tackle SDoH in IBD with the goal of improving outcomes.[12]

Although scarce, promising data exist to counter some of the health disparities resulting from SDoH. A systematic review by Schoenfeld et al[72] in 2020 found that to improve outcomes for patients with IBD, a holistic approach comprising a multidisciplinary team founded on structured monitoring, regular follow-up, patient education, and ready access to care renders patients better-resourced to receive optimal care. While this systematic review does not address the impact of multidisciplinary teams on SDoH in IBD care, elements of this study, such as close monitoring, education, and a closed-loop system, may help alleviate structural and cultural barriers among minoritized groups with IBD. Studies like these are needed to employ tactics that bring the medical field closer to effectively practicing culturally sensitive and inclusive care.[73]

While many institutions train their employees on cultural competence, we propose that cultural humility and cultural sensitivity are better approaches to improve health equity in IBD care (Figure 3). Cultural competence is defined as the ability to practice in a manner that affirms and values the worth of individuals while preserving their dignity.[74,75] It emphasizes possessing certain sets of skills and knowledge related to different cultures. On the other hand, cultural humility suggests focusing on recognizing the limitations of one's own knowledge and understanding.[74,75] This shifts the focus from the patient and puts the onus on the healthcare professional who is striving to continually expand their cultural awareness. Cultural sensitivity involves awareness of the cultural differences and needs of individuals and their communities. This emphasizes empathy, understanding, and adaptability when working with diverse individuals.[74,75]

Train Healthcare Professionals in Cultural Humility

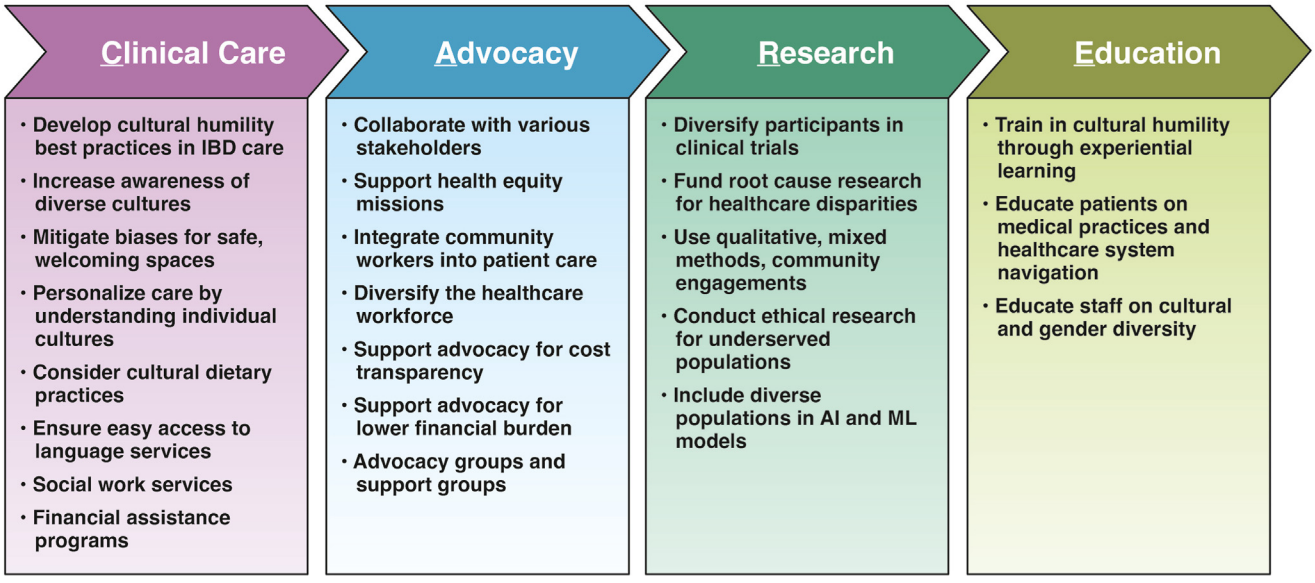
Training in cultural humility may be one of many potential solutions toward improving the delivery of care to minoritized communities with IBD. Recent understanding of healthcare disparities has prompted a shift from the concept of achieving "competence" to emphasizing "cultural humility." Moving away from the impossible task of mastery of culture-specific care, cultural humility calls for the employment of sensitivity to and recognition of the complexity of a patient's cultural identity and intersectionality, and engagement in an ongoing learning process from individual patient experiences.[76] As a result, traditional cultural competency training may inadvertently reinforce stereotypes and foster an "us vs them" mentality, overshadowing individual patient differences.[76]

Despite increased recognition of the role of cultural humility in improving patient care, there are no studied strategies targeting cultural humility achievement in historically disadvantaged populations with IBD. One qualitative study explored the experiences of South Asian patients with IBD, revealing significant cultural and religious beliefs posing additional challenges to their care, such as dietary preferences, family roles, and travel-related obstacles.[77] This study underscores the need to investigate cultural barriers affecting diverse communities with IBD and develop improved healthcare models that prioritize cultural humility over traditional cultural competency training.

Incorporate Culturally Sensitivity in Clinical Care

As our country grows increasingly racially and ethnically diverse, the employment of culturally sensitive and inclusive care is a critical step in closing IBD health and healthcare disparity gaps, and a necessary step to the delivery of high-quality, equitable care to all patients living with IBD. Furthermore, as more younger individuals are coming out as LGBTQ+, healthcare professionals will encounter more sexual and gender minority populations with IBD in their clinical practice.[43] Therefore, a more inclusive breadth of training and education in IBD care and best practices are essential to promote culture humility and health equity.[9]

To practice cultural humility and competence, providers need to be aware of the diverse cultures that they serve and alter and adapt their practice to welcome historically disadvantaged communities.[78] Healthcare



AI, artificial intelligence; ML, machine learning.

Figure 3. C.A.R.E. in IBD: culturally sensitive and inclusive care in IBD. A summary of some tips to establishing a culturally sensitive approach to IBD care through 4 pillars of clinical care, advocacy, research, and education.

providers should be aware of upstream SDoH like government policies, immigration laws, voting restrictions, and anti-transgender laws that may result in health inequity for some marginalized individuals. On an institutional level, showcasing advocacy groups and resources (Table 2) that promote cultural humility and inclusivity intentionally and unabashedly and having national societies provide platforms for such organizations to highlight their work serves the important purpose of giving a voice to those historically marginalized. As it relates to personally mediated changes, mitigating bias and creating a safe and welcoming professional space for patients and staff (ie gender-neutral bathrooms, pronoun identifiers in electronic medical records, and using gender-neutral language) affirms inclusivity and cultural sensitivity. Therefore, it is incumbent on physicians to provide both active and passive indicators of their respect for LGBTQ+ identified people—a rainbow pin, poster announcing allyship, use of nonjudgmental language, including the inquiry and use of a patient's preferred pronouns and chosen name.

Other actionable practices that might benefit individuals from diverse racial and ethnic backgrounds include understanding the diverse cultures to which individuals belong. When providing counseling on IBD-related treatments, clinicians should keep an open mind in understanding an individual's culture, allowing for a more personalized treatment plan while honoring

Table 2. Advocacy Groups and Organizations Promoting Health Equity in IBD and Gastroenterology

Organization	Mission	Website
Association of Black Gastroenterologists and Hepatologists (ABGH)	To promote health equity in Black communities, advance science, and develop the careers of Black gastroenterologists, hepatologists, and scientists.	www.blackingastro.org
Color of Gastrointestinal Illness (COGI)	To improve the quality of life for BIPOC who are affected by IBD, digestive disorders, and associated chronic illnesses through community, research, education, and advocacy.	www.colorofgi.org
Crohn's and Colitis Foundation (CCF)	To cure Crohn's disease and ulcerative colitis, and to improve the quality of life of children and adults affected by these diseases.	www.crohnscolitisfoundation.org
Girls with Guts	To support and empower women with IBD and/or ostomies through the building of sisterhood and self-esteem.	www.girlswithguts.org
Crohn's and Colitis Young Adults Network	To support young adults who have been diagnosed with Crohn's disease or ulcerative colitis.	www.ccyanetwork.org/
Rainbows in Gastro (RIG)	To increase the visibility of SGM providers in the field of gastroenterology and hepatology and engage with the SGM community to guide education, advocacy, and research (Community, Healing, Advocacy, Research, and Mentorship).	www.x.com/rainbowingastro
South Asian IBD Alliance (SAIA)	To create resources, research, and education for IBD patients and healthcare providers of South Asian origin to minimize disparities, dispel stigma, and promote early diagnosis and improve access to treatment.	www.southasianibd.org
Voice for IBD	To advocate for Hispanic and Latinx patients with IBD and committed to finding a cure.	www.threads.net/@voiceforibd
FUNEIICO (Fundación de Enfermedad Inflamatoria Intestinal Colombiana)	To raise awareness of IBD, provide help to Spanish-speaking people who are diagnosed with ulcerative colitis and Crohn's disease, in the search for solutions for a comprehensive treatment, providing the required assistance to both patients and their families, as well as the medical body, health institutions, and those interested in the detection, knowledge, management, and treatment of these entities.	www.funeiico.com

BIPOC, Black, Indigenous, and people of color; IBD, inflammatory bowel disease; SGM, sexual and gender minority.

that individual's beliefs and culture. For example, in some cultures, IBD might be perceived as a taboo, which results in increased isolation of that patient.[77] Therefore, IBD clinicians would need to spend time raising awareness and further education on living with IBD including educating family members. Additionally, dietary concerns can change among the diverse racial and ethnic groups with IBD. When counseling about diet in IBD, providers need to take into consideration cultural and religious dietary practices. Furthermore, clinics should have easily accessible language services to help with medical interpretation for individuals who do not speak English. IBD clinics should also be aware that some patients might face major barriers in terms of transportation, childcare services or taking time off work for medical procedures or visits. Proposed solutions include expanding clinic hours, providing reimbursement for childcare or transportation or providing access to virtual care.[79] Assessing these system-wide implementations formally through metrics will allow for impactful change in outcomes that can be measured and reproduced.

Diversify the IBD Healthcare Workforce

Studies show that diversity in the healthcare workforce improves patient outcomes, particularly in historically disadvantaged communities, likely in part resulting from culture-congruent care.[80,81] Despite this observation, the medical field fails to mirror the increasingly diverse populations it serves. For example, data from the 2022 Physician Specialty Data Report[82] showed that fewer than 10% of physicians in the United States were either Hispanic/Latinx or Black, despite these racial/ethnic group comprising over 30% of the U.S. population.[82] In a 2022 multi-gastroenterological society publication study entitled, "Diversity, Equity and Inclusion in Gastroenterology and Hepatology: A Survey of Where We Stand," the most frequently reported barriers to increasing racial and ethnic diversity in gastroenterology and hepatology were insufficient representation of underrepresented racial and ethnic minority groups in the education and training pipeline (n = 431 [35.4%]), in professional leadership (n = 340 [27.9%]), and among practicing gastroenterology and hepatology professionals (n = 324 [26.6%]).[83] Therefore, in order to improve the delivery of care for historically disadvantaged communities, including those living with chronic, complex digestive diseases like IBD, efforts to recruit and retain healthcare professionals from underrepresented groups in medicine and those that represent the community in the proximity that surrounds hospital systems where such patients rely on for care is important.

Improving Representation in IBD Research

Recruitment of minoritized participants in IBD clinical trials should focus on mitigating bias of research team members, community engagement, and other culturally tailored approaches[84] that reflect an understanding of the populations in which recruitment is desired. Hiring language congruent coordinators and research staff may help ameliorate some of the cultural barriers that may exacerbate hesitancy in enrollment in research. Incentivizing research that identifies the unique sociocultural barriers that extend what is known about SDoH in historically disadvantaged communities with IBD, and targeted initiatives to fund research from underrepresented groups in medicine that have been woefully underfunded may also result in improved understanding of how best to tackle barriers and resultant disparities.[85,86] Considering the employment of qualitative, mixed methods, and community engagement research methods[87,88] in order to reach and better understand historically disadvantaged communities may also prove helpful. Additionally, when conducting research in historically disadvantaged communities, understanding the regulatory protocols for these specific communities, such as Tribal Institutional Review Boards in Indigenous communities, is of great importance.[89]

In IBD research more generally, including more expansive demographic data and referencing the lack of diversity of participants as a study limitation and formally acknowledging unexplained differences among racial and ethnic groups in study outcomes provide an opportunity to advance science and fund areas for understanding such disparities.[73,90] Finally, formally including historically disadvantaged patients in research endeavors, not only as participants, but also as stakeholders working in collaboration with physicians and researchers, may offer unique insight and perspective on how best to address the complexities of care that have been historically underappreciated and under addressed in such populations.[91]

Therefore, policies that fund community engagement for research, adopt recruitment efforts to attract historically disadvantaged researchers and participants with intentionality and without bias, and execute strategies to bring clinical trials to community and rural settings should be implemented.

Conclusion

The epidemiology of IBD is everchanging and impacts individuals of diverse races, ethnicities, genders, sexual orientations, and socioeconomic statuses. As more research emerges on health disparities and SDoH in historically disadvantaged communities with IBD, many opportunities exist to address these disparities in care and develop actionable plans to change the systems to avoid propagating these disparities. To achieve health equity in IBD, healthcare systems and professionals should consider cultural sensitivity and humility to understand the intersectionality of an individual's identities, the upstream, midstream, and downstream factors

impacting an individual's health, and the resources available to mitigate these barriers. As we look at the future of IBD care in a rapidly changing world with exponential advances in IBD, cultural sensitivity, cultural humility, and diversity, equity, and inclusion must be integrated into the framework of every aspect of IBD care including patient care, education, research, and innovation.

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Modern Advanced Therapies for Inflammatory Bowel Diseases: Practical Considerations and Positioning

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The therapeutic armamentarium for management of inflammatory bowel diseases has expanded dramatically in the last 5 years, with the introduction of several medications with different mechanisms of action. These include the oral small molecule drugs Janus kinase inhibitors (including upadacitinib, approved for Crohn's disease and ulcerative colitis [UC], and tofacitinib, approved for UC) and sphingosphine 1-phosphate receptor modulators (ozanimod and etrasimod, both approved for UC), and biologic agents, such as selective interleukin-23 antagonists (risankizumab approved for Crohn's disease, and mirikizumab approved for UC). The efficacy and safety of these therapies vary. In this review, we discuss practical use of these newer advanced therapies focusing on real-world effectiveness and safety data, dosing and monitoring considerations, and special situations for their use, such as pregnancy, comorbid immune-mediated disease, use in hospitalized patients with acute severe UC, and in the perioperative setting. We also propose our approach to positioning these therapies in clinical practice, relying on careful integration of the medication's comparative effectiveness and safety in the context of an individual patient's risk of disease- and treatment-related complications and preferences.

Keywords: Crohn's Disease; Ulcerative Colitis; Positioning; Patient Assistance.

Over the last decade, treatment options for the management of inflammatory bowel diseases (IBD) have expanded remarkably. Currently, 5 different classes of advanced therapies including biologic agents and targeted oral small molecule drugs with unique mechanisms of action have been approved for the management of IBD: tumor necrosis factor (TNF)-α antagonists (infliximab, adalimumab, golimumab, certolizumab pegol), anti-integrin agents (vedolizumab, natalizumab), interleukin (IL)-12/23p40 antagonists (ustekinumab), IL23p19 antagonists (risankizumab, mirikizumab), Janus kinase inhibitors (JAKi; tofacitinib, upadacitinib and filgotinib [approved in Europe]) and sphingosine 1-phosphate receptor (S1PR) modulators (ozanimod, etrasimod).

In this review, we present practical considerations for incorporating newer non-TNF-targeting advanced therapies in clinical practice, based on our collective experience and interpretation of evidence on efficacy and real-world effectiveness and safety.

Janus Kinase Inhibitors

JAKi are oral small-molecule drugs that inhibit the transcription of proinflammatory cytokines. This inhibition is variably selective: tofacitinib, which was Food and Drug Administration (FDA)-approved to treat ulcerative colitis (UC) in 2018, primarily inhibits JAK1 and JAK3, and upadacitinib, which was FDA-approved to treat UC in 2022 and Crohn's disease (CD) in 2023, primarily inhibits JAK1. The FDA labels for JAKi state these medications are indicated for patients with failure of, or contraindications to, use of TNF antagonists. Details of the trials that led to regulatory approval of these medications are discussed elsewhere.[1,2]

Real-World Effectiveness

Tofacitinib. The overall effectiveness of tofacitinib in real-world cohorts is largely similar to the efficacy observed in clinical trials. In a systematic review and meta-analysis of 17 cohort studies with 1162 patients with UC, approximately two-thirds of patients achieved response and one-third achieved remission within 8 weeks, with higher rates observed in patients naive to biologic agents.[3] Although head-to-head clinical trials are lacking, real-world comparative studies suggest that tofacitinib may be more effective than vedolizumab in patients with UC with prior failure of TNF antagonists.[4–6] Similarly, tofacitinib was also more effective than

Abbreviations used in this paper: **ALC, absolute lymphocyte count; ASUC, acute severe ulcerative colitis; CD, Crohn's disease; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; IL, interleukin; IV, intravenous; JAKi, Janus kinase inhibitors; MACE, major adverse cardiovascular events; S1PR, sphingosine 1-phosphate receptor; SC, subcutaneously; TNF, tumor-necrosis factor; UC, ulcerative colitis; VTE, venous thromboembolism.**

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ustekinumab in patients with UC with prior failure of TNF antagonists and vedolizumab.[7]

Upadacitinib. Given the recency of its approval, there are limited real-world data on upadacitinib. In patients with UC, upadacitinib achieves high rates of clinical response and remission, exceeding 80% in some real-world cohorts despite a multidrug refractory population.[8,9] In patients with CD with previous failure of TNF antagonists, vedolizumab and ustekinumab, 64% of patients treated with upadacitinib achieved clinical response and 27% achieved clinical remission at 3 months.[10] Upadacitinib may be particularly more effective in patients with colon-dominant CD, and the clinical trials program demonstrated efficacy in perianal disease.[11] Although there are no head-to-head data comparing upadacitinib and tofacitinib in patients with UC, real-world studies suggest upadacitinib may be more effective than tofacitinib in patients with UC and may provide benefit even in patients with prior tofacitinib failure.[8,9] Based on these data, in our practice, upadacitinib has become the preferred JAKi.

Dosing and Onset of Action

The efficacy and safety of JAKi are dose dependent. Therefore, the optimal dose is the lowest dose that achieves and maintains remission. Both tofacitinib and upadacitinib have rapid onset of action, with a substantial proportion of patients with UC seeing clinical improvement within 1–3 days of starting therapy, faster than several other advanced therapies.[12–14] Similarly, in patients with CD, upadacitinib can reduce abdominal pain and stool frequency within 1 week of treatment initiation in clinical trials.[15]

Tofacitinib. The tofacitinib induction dose for outpatients with moderate-severe UC is 10 mg twice daily (or 22 mg extended release daily) for 8 weeks; more than half of patients who have inadequate clinical response at 8 weeks may improve with an additional 8 weeks of induction therapy (delayed responders).[16] (FDA approval of the extended release formulation was based on indirect data rather than specific studies in UC.[17]) Following induction therapy, patients may be maintained on 10 mg twice daily, or decreased to 5 mg twice daily (alternatively, 11 mg extended release daily). Although the FDA recommends trying to maintain remission with 5 mg twice daily, in clinical practice, up to 50% of patients may lose response on de-escalation to 5 mg twice daily and half of these patients may not be able to recapture response with re-escalation to 10 mg twice daily.[18,19] In the RIVETING trial of patients with UC in stable remission on tofacitinib 10 mg twice daily for >2 years, patients with prior exposure to TNF antagonists and those with mild endoscopic activity at time of de-escalation (Mayo endoscopy score 1 vs 0) were more likely to relapse on de-escalation to 5 mg twice daily at 30 months.[20,21] In our practice, most patients treated with tofacitinib after prior exposure to TNF antagonists are continued on 10 mg twice daily for maintenance of remission; we typically consider dose de-escalation only in patients who have achieved biochemical, endoscopic, and/or histologic remission, and subsequently monitor clinically and biochemically (with stool calprotectin) following dose reduction. Table 1 summarizes typical dosing regimens, and Table 2 presents monitoring before starting therapy and while on drug.

Upadacitinib. The upadacitinib induction dose for outpatients with moderate-severe UC and CD is 45 mg daily for 8 and 12 weeks, respectively. Similar to tofacitinib, approximately 60% of patients with UC with inadequate clinical response to induction therapy at 8 weeks may benefit from extended induction dosing for an additional 8 weeks (delayed responders).[22] Data on efficacy of extended induction in patients with CD are awaited. Following induction, both upadacitinib 15 mg daily and 30 mg daily are approved doses for maintenance in UC and CD. Numerically, upadacitinib 30 mg daily may be more effective especially in patients with prior failure of TNF antagonists and is the typical maintenance dose for most patients in our practice; a subset of patients who achieve clinical, endoscopic, and/or histologic remission and who are at higher risk of adverse events may be de-escalated to maintenance therapy with 15 mg daily. With regard to dose escalation, in the UC long-term extension study, patients with inadequate response to upadacitinib 15 mg daily could increase to 30 mg daily, and 30% of these patients achieved clinical remission at Week 48.[23]

Safety

Cardiovascular and thromboembolism risk. JAKi carry FDA black-box warnings regarding increased risk of mortality, major adverse cardiovascular events (MACE), thrombosis, malignancy, and serious infections. In the Oral Rheumatoid Arthritis (ORAL) Surveillance trial, patients with active rheumatoid arthritis despite methotrexate, who were $\geq$ 50 years old, and had at least 1 cardiovascular risk factor (current smoking, hypertension, high-density lipoprotein cholesterol level of <40 mg/dL, diabetes mellitus, family history of premature coronary heart disease, extraarticular rheumatoid arthritis, or history of coronary artery disease), were randomized to tofacitinib (5 mg twice daily and 10 mg twice daily) versus TNF antagonists to compare safety of these agents.[24] During a median follow-up of 4 years, patients treated with tofacitinib had higher rates of MACE (vs TNF antagonists: 3.4% vs 2.5%), malignancy (4.2% vs 2.9%), venous thromboembolism (VTE; 1.8% vs 0.7%), serious infection (17.7% vs 8.2%), and herpes zoster (12.3% vs 4.0%), with higher rates of adverse events observed in patients receiving the 10 mg twice daily dose. In post hoc analyses, excess risk of malignancy and MACE was primarily limited to patients $\geq$ 65 years old and those with a history of smoking.[25] Based on the trial's findings, the FDA modified the label for all

Table 1. Dosing Strategies

	Induction	Maintenance	Intensification options[a]
Janus kinase inhibitors			
Tofacitinib[b]	10 mg twice daily or 22 mg ER daily for at least 8 wk	10 mg twice daily/22 mg ER daily OR 5 mg twice daily/11 mg ER daily	Continue or escalate to 10 mg twice daily/22 mg ER daily
Upadacitinib[b]	45 mg daily for 8 wk (UC) or 12 wk (CD)	30 mg or 15 mg daily	Extended 45 mg induction (16 wk for UC), anecdotal use of extended 45 mg dosing past 12 wk in CD or 16 wk in UC
Interleukin-23 antagonists			
Risankizumab	600 mg (CD) or 1200 mg (UC[b]) IV at wk 0, 4, 8	180 mg or 360 mg SC on-body injector every 8 wk starting at wk 12[c]	1200 mg IV "rescue dose"
Mirikizumab	300 mg (UC) or 900 mg (CD[d]) IV at wk 0, 4, 8	200 mg (UC, 2 citrate-containing prefilled pens) or 300 mg (CD[d]) SC every 4 wk	Reinduction (300 mg IV every 4 wk x 3 for UC)
Sphingosine-1 phosphate receptor modulators			
Ozanimod	7-day PO dose titration starter pack	0.92 mg PO daily (starting d 8)	None
Etrasimod	2 mg PO daily	2 mg PO daily	None

CD, Crohn's disease; ER, extended release; IV, intravenous; PO, per os; SC, subcutaneous; UC, ulcerative colitis.
[a]Intensification options are off-label and have varying degrees of supporting evidence.
[b]Tofacitinib and upadacitinib labels recommend dose reduction in cases of renal or hepatic impairment. For upadacitinib, dose reduction is recommended only for glomerular filtration rate <30 mL/minute or severe hepatic impairment, whereas for tofacitinib, dose reduction is recommended for moderate hepatic or moderate renal dysfunction.
[c]Authors prefer 360 mg in CD.
[d]Not Food and Drug Administration–approved for this indication.

Table 2. Therapy Preparation and Monitoring Checklist

	Pretherapy	Induction	Maintenance
Janus kinase inhibitors	o CBC with differential o Hepatic panel o Creatinine o Lipid panel o Latent TB testing o Chronic viral hepatitis panel o Recommend recombinant herpes zoster vaccine series	o Lipid panel o Consider CRP and calprotectin to inform extended induction candidacy and maintenance dose selection o Finish recombinant herpes zoster vaccine series if not completed pretherapy	o CBC and hepatic panel every 3 mo o Yearly skin examinations
IL23 antagonists	o Hepatic panel o Latent TB testing o Chronic viral hepatitis panel	o Hepatic panel	o CBC and hepatic panel every 3–6 mo
Sphingosine-1 phosphate receptor modulators	o EKG o Eye examination Etrasimod: all patients Ozanimod: patients with diabetes, uveitis, or macular edema history o Skin examination (etrasimod) o CBC with differential o Hepatic panel o VZV antibody if no history of chickenpox or vaccination o Recommend recombinant herpes zoster vaccine series	o Blood pressure o Hepatic panel o Complete recombinant herpes zoster vaccine series (if not completed pretherapy) o Eye and skin examinations as applicable if not completed pretherapy	o CBC with differential and hepatic panel every 3 mo o Yearly skin examinations

CBC, complete blood count; CRP, C-reactive protein; EKG, electrocardiogram; IL, interleukin; TB, tuberculosis; VZV, varicella zoster virus.

JAKi used for treating patients with chronic inflammatory diseases including IBD, recommending their use only after inadequate response or intolerance to TNF antagonists. The European Medicines Agency, although not endorsing a restriction for use only in patients with prior TNF antagonist exposure, issued a recommendation that JAKi be used with caution (only in absence of suitable alternatives) in patients $\geq$ 65 years old, current or former smokers, and patients at increased risk of cancer.[26]

In contrast to rheumatoid arthritis, no increased risk of MACE, VTE, or malignancy has been observed in patients with IBD treated with tofacitinib in long-term follow-up of clinical trial programs and real-world cohort studies.[3,27] Similarly, no increased risk of MACE, VTE, or malignancy has been observed in open-label extension studies of upadacitinib for UC.[28] Comparative studies also do not suggest an increased risk of MACE with JAKi relative to other advanced therapies in patients with IBD.[29] In a real-world comparative study in patients with IBD, tofacitinib was not associated with higher risk of VTE (vs TNF antagonists: 5% vs 4%) or MACE (2% vs 1%).[30] This difference in JAKi risk may be related to the younger age and lower burden of smoking in patients with IBD, compared with the rheumatoid arthritis patient population included in the ORAL Surveillance trial. Meta-analyses do not suggest any significant differences in the safety of upadacitinib versus tofacitinib.[31] Although use of JAKi in clinical trial programs led to an increase in total cholesterol without any change in the ratio of low-density lipoprotein and high-density lipoprotein cholesterol, the clinical impact of these findings remains unclear.

Herpes zoster. In addition to increased risk of serious bacterial infections with JAKi, these agents are also associated with an increased risk of reactivation of herpes zoster in a dose-dependent manner, particularly when used in combination with corticosteroids, and this risk substantially exceeds that of other agents.[32–34] All patients receiving JAKi should receive the 2-dose recombinant herpes zoster vaccine, the first dose of which can be given either before or after commencing therapy. The Advisory Committee on Immunization Practices recommends that the recombinant zoster vaccine be given at months 0 and 1 or 2 for immunocompromised adults $\geq$19 years old. In contrast to recombinant vaccines, live vaccines should be avoided while taking a JAKi.[35]

Acne. Acne is a common adverse effect observed with JAKi, particularly upadacitinib at higher doses, occurring in about 20% of patients.[8,36] Counseling patients regarding this potential adverse effect may aid in therapy adherence. In the dermatology literature, upadacitinib is associated with a 4.8-times higher odds of acne compared with placebo.[37] Although no consistent risk factors have been identified, the risk of acne in trials of upadacitinib in atopic dermatitis seems to be dose-dependent, higher in younger patients (15–40 years old), higher in females compared with males, and potentially higher in non-Whites.[38] Topical therapies can help ameliorate this side effect, typically clindamycin in combination with benzoyl peroxide, but systemic antibiotic therapy may be required in more severe cases.

Special Situations

Therapeutic drug monitoring and immunogenicity. As small molecule drugs, JAKi, unlike biologics, have short half-lives and no potential for immunogenicity. At present, therapeutic drug monitoring is not warranted, largely because of the stronger correlation between dose and exposure with small molecules as compared with biologic agents; however, research examining the role of drug monitoring, particularly in specific phenotypes, such as acute severe UC (ASUC), is warranted.

Pregnancy and lactation. In contrast to monoclonal antibody therapies, JAKi can cross the placenta during the first trimester and animal data suggest they should be avoided in pregnancy; human data are limited.[39] Therefore, they should be discontinued 4 weeks before attempting conception.[40] Similarly, JAKi pass into breastmilk and should be avoided while breastfeeding. In most patients who conceive while taking a JAKi, maintenance treatment should be transitioned to an agent safe in pregnancy if possible, with shared decision making taking into account patients' specific risks of disease-related complications.

Acute severe ulcerative colitis. Because of their rapid onset of action and avoidance of the challenges posed by accelerated biologic clearance seen in the setting of protein-losing colopathy, JAKi have garnered attention as possible therapies for hospitalized patients with ASUC. In a randomized trial of 104 mostly biologic-naive patients with ASUC, tofacitinib 10 mg 3 times daily with intravenous (IV) corticosteroids resulted in a higher rate of clinical response within 7 days compared with IV corticosteroids alone; however, 1 patient in the tofacitinib arm developed dural sinus thrombosis.[41] In a systematic review of 18 cohort studies or case series including 148 patients with corticosteroid-refractory ASUC with prior failure of infliximab treated with tofacitinib, 90-day colectomy-free survival was 86%.[42] In a multicenter retrospective cohort study of 25 mostly advanced therapy-experienced, oral steroid–nonresponsive patients with ASUC, upadacitinib 45 mg daily or 30 mg twice a day combined with IV corticosteroids was associated with a 90-day colectomy-free survival of 76%.[43]

Perioperative management of JAKi. In a multicenter retrospective cohort study, perioperative JAKi use was not associated with increased risk of adverse perioperative outcomes compared with other advanced therapies in patients with refractory UC undergoing total colectomy,[44] and an urgent IBD surgery should not be delayed to await JAKi washout. An American College of Rheumatology and American Association of Hip and Knee Surgeons guideline suggests JAKi be withheld for 3 days

before joint surgery, and it may be reasonable to extrapolate this to elective surgery in patients with IBD.[45] In view of rapidly relapsing inflammatory activity in joints in patients with rheumatoid arthritis after holding tofacitinib, strong consideration should be given to resuming JAKi promptly on evidence of good wound healing.[45,46]

Extraintestinal manifestations and comorbid conditions. JAKi are also approved for treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and atopic dermatitis. Hence, these agents may be especially useful in patients with comorbid inflammatory peripheral arthritis or axial spondyloarthropathies with IBD, particularly those with axial spondylarthritis for whom a key therapy alternative, anti-IL17 agents, is contraindicated. Table 3 summarizes the effectiveness of different advanced therapies for comorbid immune-mediated inflammatory conditions.

Interleukin-23 Antagonists

Monoclonal antibodies targeting the p19 subunit of IL23 are effective therapies for the treatment of CD and UC. Currently, 2 IL23 antagonists are approved by the FDA: risankizumab for moderate-severe CD, and mirikizumab for moderate-severe UC; these drugs, along with guselkumab, are at advanced phases of development and approval for CD and UC. These agents are mechanistically similar to but distinct from ustekinumab, which blocks IL12 and IL23 via inhibition of their shared p40 subunit, and these seemingly minor pharmacodynamic differences may have important clinical implications as discussed later. Key findings of pivotal trials of these medications that led to approval are presented next and details are discussed elsewhere.[2,47,48]

Effectiveness

Risankizumab. Risankizumab was approved for treatment of moderate-severe CD in 2022 based on 2 phase 3, 12-week induction trials (ADVANCE and MOTIVATE), and a 52-week maintenance trial (FORTIFY).[49,50] Since the approval of risankizumab, a few cohort studies have confirmed its real-world effectiveness. In a multicenter Belgian cohort study of 69 patients refractory to multiple therapies (86% exposed to $\geq$4 different advanced therapies; 99% exposed to ustekinumab, 14 with an ostomy), 62% of patients experienced clinical improvement and 18% achieved corticosteroid-free clinical remission at 24 weeks.[51] Similarly, in a French cohort of 100 patients with multidrug refractory CD, 79% achieved clinical response and 46% achieved corticosteroid-free clinical remission with risankizumab at Week 12; comparable rates were observed in a US referral center cohort.[52,53]

In a landmark head-to-head trial comparing risankizumab with ustekinumab in patients with moderate-severe CD with prior exposure to TNF antagonists (SEQUENCE), risankizumab was noninferior and superior to ustekinumab in achieving clinical remission at Week 24 (59% vs 40%) and endoscopic remission at Week 48 (32% vs 16%).[54] Based on these findings, in our practice, risankizumab has become the preferred non-TNF biologic for most patients with moderate-severe CD, either naive or exposed to TNF antagonists.

Key findings from the INSPIRE trial of induction therapy and COMMAND trial of maintenance therapy of risankizumab versus placebo in patients with moderate-severe UC suggest that risankizumab is an efficacious therapy for management of biologic-naive and biologic-exposed patients with moderate-severe UC, with 21% of risankizumab-treated patients achieving remission compared with 6% of placebo-treated patients at Week 12.[55,56] Patients with prior ustekinumab exposure were excluded. FDA approval of risankizumab for UC is anticipated in the latter half of 2024.

Mirikizumab. Mirikizumab was approved for the treatment of moderate-severe UC in 2023 based on the phase 3, 12-week induction trial, LUCENT-1, and the 40-week maintenance trial, LUCENT-2.[57] Approximately 40% of patients in LUCENT-1 and LUCENT-2 had failed a

Table 3. Overlapping Medication Effectiveness in Common Comorbid Immune-Mediated Diseases

	Plaque psoriasis	Atopic dermatitis	Rheumatoid arthritis	Psoriatic arthritis	Axial spondylarthritis	Multiple sclerosis
Tofacitinib	☑	☑	☑	☑	☑	
Upadacitinib	☑	☑	☑	☑	☑	
Ozanimod						☑
Etrasimod						[a]
Risankizumab	☑			☑		
Mirikizumab	☑			[a]		
Guselkumab	☑			☑		

[a]Data gap.

prior biologic or tofacitinib, although patients with prior exposure to ustekinumab were excluded. At Week 12, a significantly higher proportion of mirikizumab-treated patients achieved clinical response (vs placebo, 64% vs 42%), clinical remission (24% vs 15%), and endoscopic remission (36% vs 21%). In total, 80% of mirikizumab-treated patients responded by Week 24. Among Week 12 responders who continued mirikizumab, 51% and 58% of patients achieved clinical remission and endoscopic improvement at Week 52, respectively. At this time, there are no published real-world data on mirikizumab in UC.

Data from the pivotal phase 3 trial of mirikizumab in patients with moderate-severe CD recently were presented.[58] In the 52-week, treat-through VIVID-1 trial, adult patients were randomized 6:3:2 to mirikizumab 900 mg IV every 4 weeks for 3 doses, followed by 300 mg subcutaneously (SC) every 4 weeks from Week 12 to Week 52, placebo, or ustekinumab ~6 mg/kg IV at Week 0 followed by 90 mg SC every 8 weeks from Week 8 to Week 48. At Week 52, mirikizumab was superior to placebo (clinical remission, 54% vs 20%; endoscopic remission, 29% vs 4%) and noninferior to ustekinumab (clinical remission, 54% vs 48%; endoscopic remission, 29% vs 28%). In the subset of patients with prior exposure to biologics, mirikizumab was comparable with ustekinumab in achieving clinical remission (51% vs 42%; $P = .08$) and endoscopic response (45% vs 40%; $P = .35$). Regulatory approval of mirikizumab for CD is awaited.

Guselkumab. Complete phase 3 data for induction and maintenance for guselkumab for CD and UC are currently awaited. In the phase 2 GALAXI-1 trial in patients with moderate-severe CD, rates of achieving clinical and endoscopic outcomes with guselkumab were significantly higher than placebo, and numerically higher than those observed with ustekinumab as a nonpowered active reference arm at Weeks 12 and 48.[59,60] In the QUASAR phase 3 induction trial of guselkumab for moderate-severe UC, guselkumab 200 mg IV every 4 weeks for 3 doses was more effective than placebo in achieving clinical remission at Week 12 (23% vs 8%).[61]

Dosing and Onset of Action

Risankizumab. The approved dosing for risankizumab in patients with moderate-severe CD is 600 mg IV at Weeks 0, 4, and 8, followed by SC dosing via an on-body injector with 360 mg or 180 mg every 8 weeks starting at Week 12. In our practice, most patients transition to 360 mg SC dosing after completion of induction therapy given numerically higher rates of response, especially in multidrug refractory patients, with the higher dose.

In patients in the phase 3 CD trials with inadequate response at Week 16 or later, an additional 1200-mg IV dose as rescue was permitted twice at least 16 weeks apart, and 20%–36% who received rescue therapy achieved clinical remission.[62] In practice, a 1200-mg IV dose may be difficult to obtain from payors because it is not an approved dose for any indication at present; in the absence of other data, a 600-mg dose could be substituted, particularly because 600-mg and 1200-mg doses achieved similar results in the clinical trial program. Whether escalation of SC dosing to every 4–6 weeks may be beneficial in patients with secondary loss of response to standard dose risankizumab is an outstanding question; in a small case series of 12 patients who underwent dose escalation, 50% of patients improved clinically.[63]

In contrast to CD, the induction dose studied in patients with moderate-severe UC is 1200 mg IV at Weeks 0, 4, and 8, followed by SC maintenance therapy (180 mg or 360 mg every 8 weeks, like CD dosing).

Risankizumab has a relatively rapid onset of action. Approximately 13% of patients achieve symptomatic remission, and 33% experience significant clinical improvement within 2 weeks of the initial IV dose.[64] Interestingly, in trials of risankizumab in moderate-severe CD, a substantial proportion of patients who achieved clinical response with risankizumab induction therapy and were subsequently randomized to placebo were able to maintain clinical remission (56%), endoscopic response (38%), and endoscopic remission (24%) at the end of 1 year, implying a high carryover effect after initial response to IV induction, particularly in patients who experience rapid clinical improvement with induction therapy.[65] Like ustekinumab, there is likely not a substantial benefit of concurrent immunomodulator treatment with risankizumab or other IL23-selective agents.

Mirikizumab. Approved dosing for mirikizumab in patients with moderate-severe UC is induction therapy with 300 mg IV at Weeks 0, 4, and 8, followed by 200 mg (given as 2 injections of 100 mg) SC every 4 weeks. Approximately 50%–60% of patients who have inadequate response to initial induction therapy, or experience secondary loss of response during maintenance therapy, may achieve response with extended induction or rescue therapy with IV mirikizumab. Mirikizumab has a relatively fast onset of action, with separation of drug versus placebo in achieving remission observed around Week 4.[66]

Safety

There is paucity of real-world studies on the safety of IL23 antagonists in patients with IBD. In clinical trials of IL23 antagonists, these agents seem to be safe with low rates of serious infection, MACE, and malignancy.[67] No specific dose-dependent or cumulative treatment duration-related safety events have been observed. None of the agents carry black box warnings. The most common adverse events observed in clinical trials (approximately 3%–14% across trials) are upper respiratory

tract infections, joint pain, injection site reactions, rash, headache, and urinary tract infection; in our practice, these adverse effects have been dose-limiting or concerning. Hypersensitivity reactions are rare (<1%). A similarly reassuring safety profile has been reported in the psoriasis literature.[68]

It is unclear whether selective IL23 antagonists are safer than ustekinumab's IL12/23 antagonism. However, ustekinumab seems to be safer than TNF antagonists and vedolizumab in patients with CD, with ~50% lower risk of serious infections compared with either agent in large real-world cohorts, findings that may reflect ustekinumab's inherent safety profile and its relative effectiveness in preventing direct and indirect inflammatory complications.[69,70]

Special Situations

Therapeutic drug monitoring and immunogenicity. The risk of immunogenicity with IL23 antagonists is very low. In the pivotal phase 3 trials of risankizumab, only 1%–2% of patients developed antibodies to risankizumab, most nonneutralizing, and their presence did not impact exposure or clinical outcomes.[49,50] There are very limited data on the correlation between drug concentrations and clinical outcomes in risankizumab-treated patients. In a small real-world study, risankizumab drug concentrations were higher in patients in biochemical remission compared with those without biochemical remission (13.8 vs 2.6 μg/mL; $P < .01$).[71] In the LUCENT trials, 23% (88/378) of mirikizumab-treated patients developed antidrug antibodies, but only 10 (2.6%) of these patients had reduced serum trough concentrations of mirikizumab.[72] Concomitant immunomodulator therapy does not seem to impact pharmacokinetics of mirikizumab in post hoc analyses. As of this writing, there are no commercially available serum drug level or antidrug antibody assays for the IL23 antagonists.

Pregnancy and lactation. There are no published pregnancy data regarding IL23 antagonists, all of which are IgG monoclonal antibodies and would be expected to cross the placenta. Data from ustekinumab-exposed pregnancies are reassuring.[73,74] Even in the absence of direct evidence, it is reasonable to continue IL23 antagonists during pregnancy. For infants exposed in utero, weighing the risks and benefits of administering pediatric live vaccines within the first 5 months (risankizumab) and 2 months (mirikuzmab), based on the respective drug half-lives, is recommended.

Acute severe ulcerative colitis. There are no data on utility of mirikizumab in hospitalized patients with ASUC; given a relatively slower onset of action compared with JAKi and infliximab, mirikizumab and other IL23 antagonists are unlikely to be effective agents for inpatient use.

Perioperative management of interleukin-23 antagonists. There are limited data on safety of IL23 antagonists in patients undergoing IBD-related surgery. Ustekinumab is not associated with increased risk of postoperative complications in small real-world studies.[75] A rheumatology and orthopedic society guideline suggests delaying elective joint surgery until the next biologic dose is due, and withholding the next dose until wound healing is observed, typically 14 days postoperatively.[45]

Extraintestinal manifestations and comorbid conditions. Risankizumab and guselkumab are approved for treatment of psoriasis and psoriatic arthritis, although typical dosing for these indications is significantly lower than those for IBD. Mirikizumab is also effective for psoriasis, but FDA approval for this indication is not being sought because of a reprioritized development strategy focusing on gastrointestinal indications.[76] Hence, these agents may be specifically useful in patients with comorbid psoriasis or psoriatic arthritis with IBD.

Sphingosine-1 Phosphate Receptor Modulators

Etrasimod and ozanimod are 2 oral S1P receptor modulators currently approved to treat moderate-severe UC. There are 5 subtypes of S1P receptors (S1P1–S1P5), with variable expression on the lymphoid, hematopoietic, and specific organ systems including the brain, heart, and gastrointestinal tract.[77] The S1PR modulators are hypothesized to work by binding the S1P receptor on immune cell surfaces. Subsequent receptor internalization prevents the cell from sensing S1P, a signaling sphingolipid important for immune cell trafficking, thus affecting immune cell migration from lymphoid organs, such as the lymph nodes to the circulatory system. By sequestering activated immune cells in the lymph nodes, S1PR modulators lead to fewer immune cells being transported to the peripheral circulation, and subsequently fewer immune cells available to travel to target sites of active inflammation, such as the colon in patients with UC. Key findings of pivotal trials of these medications that led to approval are presented next and details are discussed elsewhere.[1,2]

Effectiveness

Ozanimod. Ozanimod was approved for the treatment of moderate-severe UC in 2021 based on 2 phase 3, 10-week induction trials and a 52-week maintenance trial within the TRUE NORTH program.[78] In these trials, ozanimod, an S1PR modulator targeting S1P1 and S1P5, was superior to placebo in achieving the primary end point of Week 10 clinical remission (18% vs 6%) and key secondary end points of clinical response (48% vs 26%), endoscopic improvement (27% vs 12%), and mucosal healing (13% vs 4%). The overall rate of achieving clinical and endoscopic end points was notably higher in biologic-naive patients compared with biologic-exposed patients, with treatment differences at Week 10 of

16%, 9%, and 3% versus placebo for biologic-naive, single biologic-exposed, and multiple biologic-exposed patients, respectively.[79] There is limited published real-world experience with ozanimod. In a referral center study of 45 ozanimod-treated patients with UC, 53% achieved clinical remission by Week 10, and 25% were in clinical remission at Week 52.[80] Approximately 80% of patients experienced >50% decline in absolute lymphocyte count (ALC) within 4 weeks. Numerically, patients who experienced >75% decline in ALC (39% of cohort) within 4 weeks experienced higher rates of clinical remission compared with those with a lesser decrease in ALC.

Etrasimod. Etrasimod was approved for the treatment of moderate-severe UC in 2023. In the ELEVATE 12 and ELEVATE 52 studies, patients treated with etrasimod, an S1PR modulator targeting S1P1, S1P4, and S1P5, experienced higher rates of clinical remission at Week 12 compared with placebo (25%–27% vs 7%–15%) and key secondary end points of clinical response (62% vs 34%–41%), endoscopic improvement (31%–35% vs 14%–19%), and endoscopic improvement/histologic remission (16%–21% vs 4%–9%).[81] Similarly, at Week 52 in a treat-through design, etrasimod was more efficacious than placebo in achieving clinical remission (32% vs 7%) and endoscopic improvement (39% vs 13%). Given the recency of its approval, there are no published real-world data on etrasimod in UC.

Dosing and Onset of Action

Ozanimod. Ozanimod is prescribed with a "ramp up" dose titration during the first week of treatment, starting at oral 0.23 mg daily for the first 4 days, then 0.46 mg daily for the next 3 days, then 0.92 mg starting at Day 8 and with continued 0.92 mg dosing as maintenance.[82] This titration strategy mitigates the risk of bradycardia, which is a class effect with S1PR modulators. Before starting ozanimod, baseline electrocardiogram (to screen for preexisting conduction abnormalities and QTc prolongation), complete blood count (with special attention to ALC), liver tests, and blood pressure should be performed; in addition, in patients with a history of diabetes, uveitis, or macular edema, a fundus examination is warranted.[83] With a slow dose titration, and by virtue of its mechanism of action focusing on lymphocyte sequestration, ozanimod is relatively slower acting.[14]

Etrasimod. Etrasimod is administered orally at 2 mg daily dose throughout induction and maintenance, without dose titration.[84] Similar to ozanimod, baseline electrocardiogram, complete blood count, and liver tests are warranted. In addition, the FDA suggests that all patients undergo a fundus examination and skin cancer screening before or shortly after initiating treatment.

Safety

Because its mechanism involves lymphocyte sequestration in the lymph nodes, ALC decreases by ~50% by Week 10 with ozanimod, and by Week 2 with etrasimod; however, subsequently, ALC remains relatively stable with both S1PR modulators. Although there are no specific recommendations for ALC monitoring from the FDA, the European label recommends periodic ALC monitoring, which practically translates to measures every 3 months.[82,85] A small subset of patients may experience severe lymphopenia (ALC $<0.2 \times 10^9$/L), for which discontinuation of these medications is recommended.[82] After stopping ozanimod, ALC returns to normal after median 30 days, with 90% achieving normalization by 12 weeks; with etrasimod, 90% normalize ALC within 5 weeks, reflecting its shorter half-life. S1PR modulator use is associated with an increased risk of infections, including shingles (varicella zoster virus vaccination is recommended before starting therapy, similar to JAKi). Progressive multifocal leukoencephalopathy has been observed rarely in patients with multiple sclerosis treated with S1PR modulators; however, no cases have been seen in patients with UC, and only 1 case has been observed with ozanimod treatment for multiple sclerosis (none with etrasimod), and monitoring for JC virus antibodies is not required.[82,86,87] The lymphopenia resulting from S1PR modulator use has not been associated with increased risks of serious and/or opportunistic infections, but real-world data are needed to clarify this relationship.[88]

S1PR modulators may also decrease heart rate, but rates of symptomatic bradycardia are very low.[89] These medications are contraindicated in patients with a recent history (within 6 months) of myocardial infarction, unstable angina, stroke or transient ischemic attack, or advanced symptomatic heart failure; with Mobitz type II or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial block (unless patient has a pacemaker); or with severe untreated sleep apnea. Caution may be warranted in patients with a resting heart rate <55 or those with Mobitz type I. These medications may increase blood pressure marginally, and patients with or without hypertension should monitor blood pressure 3 months after treatment initiation and then every 6 months thereafter. Certain medications may increase risk of hypertension or can otherwise interact with the metabolism of ozanimod (eg, monoamine oxidase inhibitors).

Special Situations

Therapeutic drug monitoring and immunogenicity. As a small molecule drug, therapeutic drug monitoring is not warranted given a strong correlation between dose and exposure, in contrast to biologic agents.

Pregnancy and lactation. Currently there are insufficient data to recommend use of S1PR modulators in pregnancy. Although animal studies suggest potential harm to the fetus during organogenesis, post hoc analyses of 4131 clinical trial participants receiving ozanimod found no evidence of increased adverse pregnancy

outcomes among 56 women with UC or multiple sclerosis exposed to ozanimod during early pregnancy.[90] For patients planning pregnancy, ozanimod and etrasimod should be held for 3 months and 1 month before conception, respectively. S1PR modulators are excreted in breast milk, and although the clinical significance is unclear avoiding S1PR use while breastfeeding is recommended.[40]

Acute severe ulcerative colitis. As a slower acting medication class as compared with TNF antagonists, JAKi, and calcineurin inhibitors, S1PR modulators are probably not suited for management of ASUC. They may be useful when bridging from inpatient medications, such as cyclosporine, for maintenance of remission, although evidence is limited to case reports.[91]

Perioperative management of S1P Receptor Modulators. There are very limited data on the safety of S1PR modulators in patients with UC undergoing colectomy, or other extraintestinal surgery. The therapeutic metabolite of ozanimod has a half-life of approximately 11 days with a washout period of approximately 55 days; the half-life of etrasimod is around 30 hours with a washout period of approximately 1 week.

Extraintestinal manifestations and comorbid conditions. Ozanimod is approved for the treatment of multiple sclerosis and may be a preferred option for patients with UC with comorbid multiple sclerosis.

Positioning Modern Therapies in the Management of Inflammatory Bowel Disease

The current approach to positioning therapies for the management of moderate-to-severe IBD relies on careful integration of medication comparative effectiveness and safety in the context of an individual patient's risk of disease- and treatment-related complications, and patient preferences (mode and frequency of administration), speed of onset of action, comorbid conditions, and importantly access to affordable therapy. Effective disease control with avoidance of corticosteroids is the primary aim of treatment, with the goal of maintaining sustained remission and avoiding disease complications. Next, we present our general approach to positioning therapies in most patients with IBD; of course, several nuances influence decision-making in each specific situation.

Crohn's Disease

Integrating data from head-to-head clinical trials (eg, SEAVUE,[92] VIVID-1) with network meta-analysis and real-world comparative effectiveness and safety studies, infliximab (typically with an immunomodulator) and adalimumab are probably the most effective therapies for induction of remission in biologic-naive patients with CD, particularly in patients with more complicated phenotypes (eg, perianal disease, fistulizing and stricturing disease) and a high burden of inflammation. In patients with moderate luminal CD, with a moderate burden of inflammation, ustekinumab and risankizumab are reasonable alternatives with a superior safety profile, and are often the authors' choice.

In patients with prior failure of TNF-α antagonists, risankizumab and upadacitinib are likely the most effective therapies. Based on the SEQUENCE trial, risankizumab is more efficacious than ustekinumab in these patients; additionally, real-world data suggest that a substantial proportion of patients treated with ustekinumab may respond after switching to risankizumab. Based on multiple observational studies and indirect treatment comparisons, all of these agents seem more effective than vedolizumab as second-line therapy. Second-line therapy with a TNF antagonist may be appropriate for patients who discontinued the first TNF antagonist because of intolerance or immunogenicity (in which case the second TNF antagonist is best used in combination with an immunomodulator). The overall safety profile of risankizumab over upadacitinib, with comparable efficacy, leads us to often favor risankizumab as a second-line agent. However, in patients with high drug clearance, low albumin, colon-dominant CD, prominent inflammatory arthritis (especially axial), or perianal disease, we may favor using upadacitinib as second-line therapy after failure of TNF antagonists. Figure 1 summarizes our proposed treatment algorithm for patients with moderate-to-severe CD.

Ulcerative Colitis

Similar to CD, there is a paucity of head-to-head clinical trials of advanced therapies in patients with moderate-severe UC. Integration of data from the VARSITY trial comparing vedolizumab versus adalimumab[93] with data from regulatory trials of approved therapies and recent network meta-analyses suggests that upadacitinib is by far the most efficacious agent for most patients with moderate-severe UC.[94,95] However, FDA black box warnings have for the most part limited its use to patients with prior failure of or intolerance to TNF antagonists. Excluding upadacitinib, infliximab and vedolizumab are probably the most efficacious therapies for induction of remission in biologic-naive patients with moderate-severe UC. In most patients with moderate UC who are steroid-dependent or steroid-responsive and not at short-term risk for hospitalization, vedolizumab is generally our preferred option, although ustekinumab or mirikizumab are also considerations. We prefer infliximab (usually in combination with thiopurines at least initially) in patients with more severe disease, higher burden of inflammation, and where rapid onset of action is desired. S1PR modulators, ozanimod and etrasimod, are also efficacious and attractive first-line therapies as oral, small molecule drugs for patients failing 5-ASA

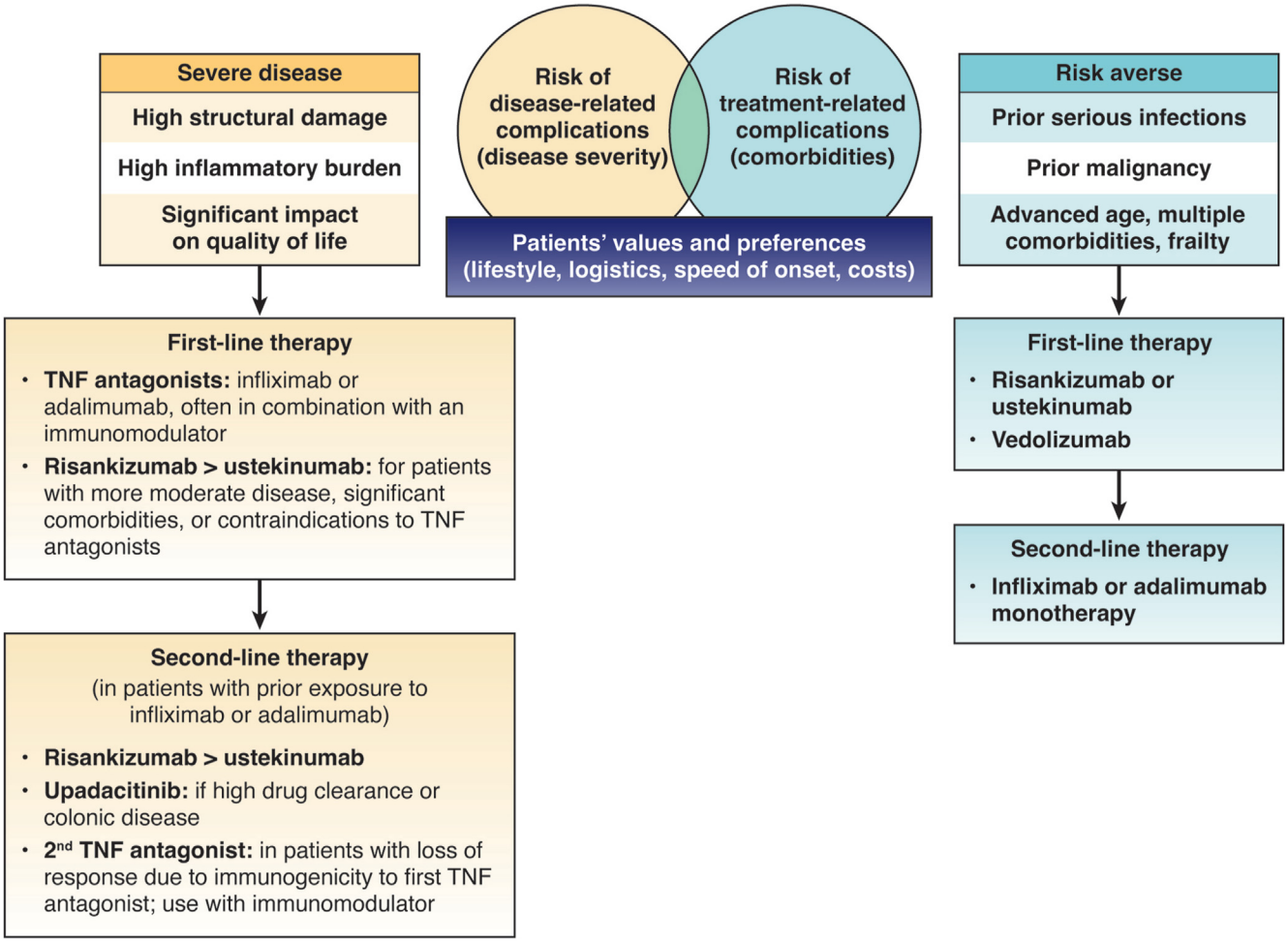

Figure 1. Proposed treatment algorithm for patients with moderate-to-severe Crohn's disease, integrating data on comparative effectiveness and safety of therapies, in the context of an individual patient's risk of disease- and treatment-related complications.

therapy, although they are more potent immunosuppressive agents with potentially higher risk of infections and, primarily in the case of ozanimod, drug-drug interactions. When used after failure of another advanced therapy, however, S1PR modulator efficacy is much diminished.

In patients who fail to respond to vedolizumab as first-line therapy, we generally prefer switching to infliximab, although ustekinumab and mirikizumab are also reasonable options. In patients with severe disease who fail first-line therapy with infliximab, we prefer upadacitinib given its high efficacy and rapid onset of action. Upadacitinib has largely replaced tofacitinib in our practice except in cases of cost or access considerations or in patients who are already in stable remission on tofacitinib. However, in older patients at higher risk of MACE and/or VTE who may have more moderate UC, ustekinumab or mirikizumab may be preferred alternatives over JAKi. In patients who discontinue infliximab because of intolerance or concern for side effects, most alternative agents are likely to be effective. Future head-to-head trials and precision medicine initiatives will help more accurately select and position therapies in patients with IBD. Figure 2 summarizes our proposed treatment algorithm for patients with moderate-to-severe CD.

Cost and Access Considerations

Cost is a major determinant of access to IBD therapies. Patients with commercial insurance are often eligible for manufacturer copay assistance programs, which often lower out-of-pocket costs to $5 or less, and bridge programs that provide free medication while navigating prior authorization denials. Medicare prescription drug reform legislation caps patient out-of-pocket costs at $2000 annually in 2025, which will improve access to injectable and orally administered medications in older or disabled patients.[96] The availability of an adalimumab biosimilar on www.costplusdrugs.com may also decrease the cost of this medication for some patients with high copays for non-infusible medications. Table 4 lists patient assistance programs available through the drug manufacturers for advanced therapies.

For all advanced therapies, patients often face delays in initiating therapy while awaiting payor approvals or

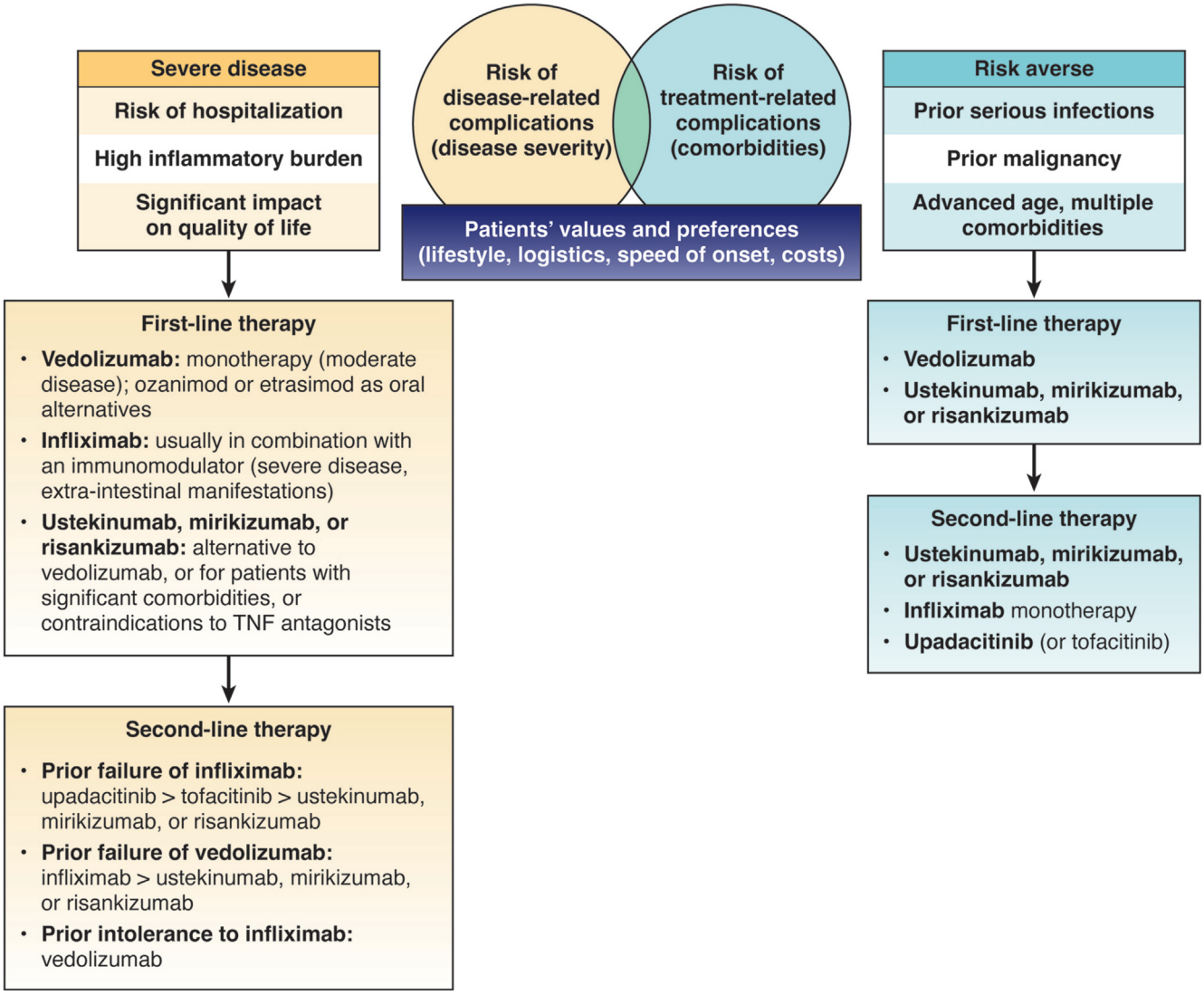

Figure 2. Proposed treatment algorithm for patients with moderate-to-severe ulcerative colitis, integrating data on comparative effectiveness and safety of therapies, in the context of an individual patient's risk of disease- and treatment-related complications.

Table 4. Patient Assistance Programs for Novel Advanced Therapies in Patients With Inflammatory Bowel Diseases

Medication	Manufacturer financial assistance program[a]
Tofacitinib	https://www.xeljanz.com/savings-and-support/
Upadacitinib	https://www.rinvoq.com/resources/save-on-rinvoq-costs
Ozanimod	https://www.zeposia.com/ulcerative-colitis/copay
Etrasimod	https://www.velsipity.com/savings-and-support
Risankizumab	https://www.skyrizi.com/skyrizi-complete/landing/crohns-about-skyrizi-complete
Mirikizumab	https://www.omvoh.com/savings-support

[a]For eligible commercially insured patients.

navigating appeals of payor denials; these delays often require patients bridge with steroids and can result in adverse outcomes.[97–99] The logistical challenge for IL23 antagonists and SC formulations of vedolizumab and infliximab can be double: the process of insurance approval for initial infusion induction therapy is followed by the approval process for SC maintenance therapy, presenting more chances for a denial to interrupt a therapy plan compared with a drug given via a single route.

Concerted advocacy efforts through major organizations, such as the Crohn's and Colitis Foundation, the American Gastroenterology Association, and the American College of Gastroenterology, have helped reduce barriers and improve access to these advanced therapies, although more work is still needed.[100]

In summary, treatment options for IBD have expanded rapidly, giving hope to millions of patients

with IBD to avoid disability caused by disease activity and disease-related complications. An integrated synthesis of risk-benefit from diverse evidence sources including head-to-head trials and real-world evidence, incorporating patients' values and preferences, can inform optimal positioning of therapies to improve patient outcomes. In the future, prognostic and predictive biomarkers in conjunction with clinical factors may help facilitate precise therapy selections.

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IBD Matchmaking: Rational Combination Therapy

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A growing number of patients with Crohn's disease and ulcerative colitis have disease that is refractory to multiple advanced therapies, have undergone multiple surgeries, and require further treatment options. For this reason, there has been increasing use of multiple simultaneous advanced targeted therapies. Although the knowledge on combined advanced targeted therapy (CATT) in inflammatory bowel disease (IBD) has been largely limited to observational data and early-phase randomized controlled trials, combination of therapies is commonplace in many other diseases. This review discusses conceptual frameworks of CATT in IBD, provides context of combined therapies in other diseases, provides current evidence for CATT in IBD, and projects future applications and positioning of CATT using existing, novel, and orthogonal mechanisms of action. CATT aims to address the need to overcome low efficacy rates and frequent loss of response of current individual therapies. Both treatment exposure and disease duration are major determinants of response to therapy. Identification of safe and effective CATT may impact positioning of this strategy to apply to a broader IBD population.

Keywords: Biologics; Combination; Dual; Simultaneous.

Conceptual Frameworks for Advanced Targeted Therapy in IBD

The pathophysiology of inflammatory bowel disease (IBD) involves an aberrant immune response against commensal gut microbes that may be influenced by environmental factors and genetic susceptibility.[1] Virtually all currently approved drugs for IBD target some aspect of the immune response, which can be subdivided into innate and adaptive immune components. Innate immune cells, which express invariant receptors that detect microbial patterns or products, include macrophages, dendritic cells, and innate lymphoid cells. Adaptive immune cells include B and T lymphocytes, which express highly diverse receptors that recognize specific antigens, as well as mucosal-associated invariant T (MAIT) cells, which express a more limited set of antigen receptors.

Therapies against IBD can be broadly categorized into groups with 1 of 4 general mechanisms of action (MOAs) (Figure 1). The first group includes untargeted drugs that suppress inflammation; examples include corticosteroids, 5-aminosalicylic acid/mesalamine, and thiopurines (eg, azathioprine, mercaptopurine). Drugs in the second group target cytokines that directly promote inflammation and/or induce the differentiation or maintenance of inflammatory immune cells.[2] This group includes therapies with MOAs antagonizing tumor necrosis factor (TNF), interleukin (IL)-12 and/or IL-23. Infliximab, adalimumab, golimumab, and certolizumab neutralize TNF, a cytokine that is produced by diverse immune and stromal cell populations (eg, macrophages, dendritic cells, T cells, and fibroblasts). TNF exerts numerous effects in the inflamed mucosa in IBD, including promoting tissue destruction and inflammatory cytokine production by T cells and macrophages.[2] Ustekinumab targets the shared p40 subunit of IL-12 and IL-23, thereby neutralizing both cytokines. By contrast, guselkumab, risankizumab, and mirikizumab selectively target the unique p19 subunit of IL-23.[3]

Drugs in the third group utilize a MOA that simultaneously blocks multiple cytokine-signaling pathways via inhibition of Janus kinases (JAKs). For example, tofacitinib targets JAK3, which mediates signaling of g chain cytokines (eg, IL-2, IL-4, IL-7, IL-9, IL-15), along with JAK1, which mediates signaling of g chain cytokines, gp130 family cytokines (eg, IL-6, IL-11, oncostatin M, and

Abbreviations used in this paper: **bDMARDs, biologic disease modifying antirheumatic drugs; CATT, combined advanced targeted therapy; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte associated protein 4; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; FMT, fecal microbiota transplant; EGFR, epidermal growth factor receptor; IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease; HER-2, human epidermal growth factor receptor 2; IL, interleukin; JAK, Janus kinases; KRAS, Kirsten rat sarcoma gene; MAIT, mucosal-associated invariant T; MAdCAM-1, mucosal addressin cell, adhesion molecule-1; MOA, mechanism of action; MTX, methotrexate; PD-1, programmed cell death protein 1; RA, rheumatoid arthritis; Treg, regulatory T; S1PRs, sphingosine 1-phosphate receptors; SAE, serious adverse event; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule-1.**

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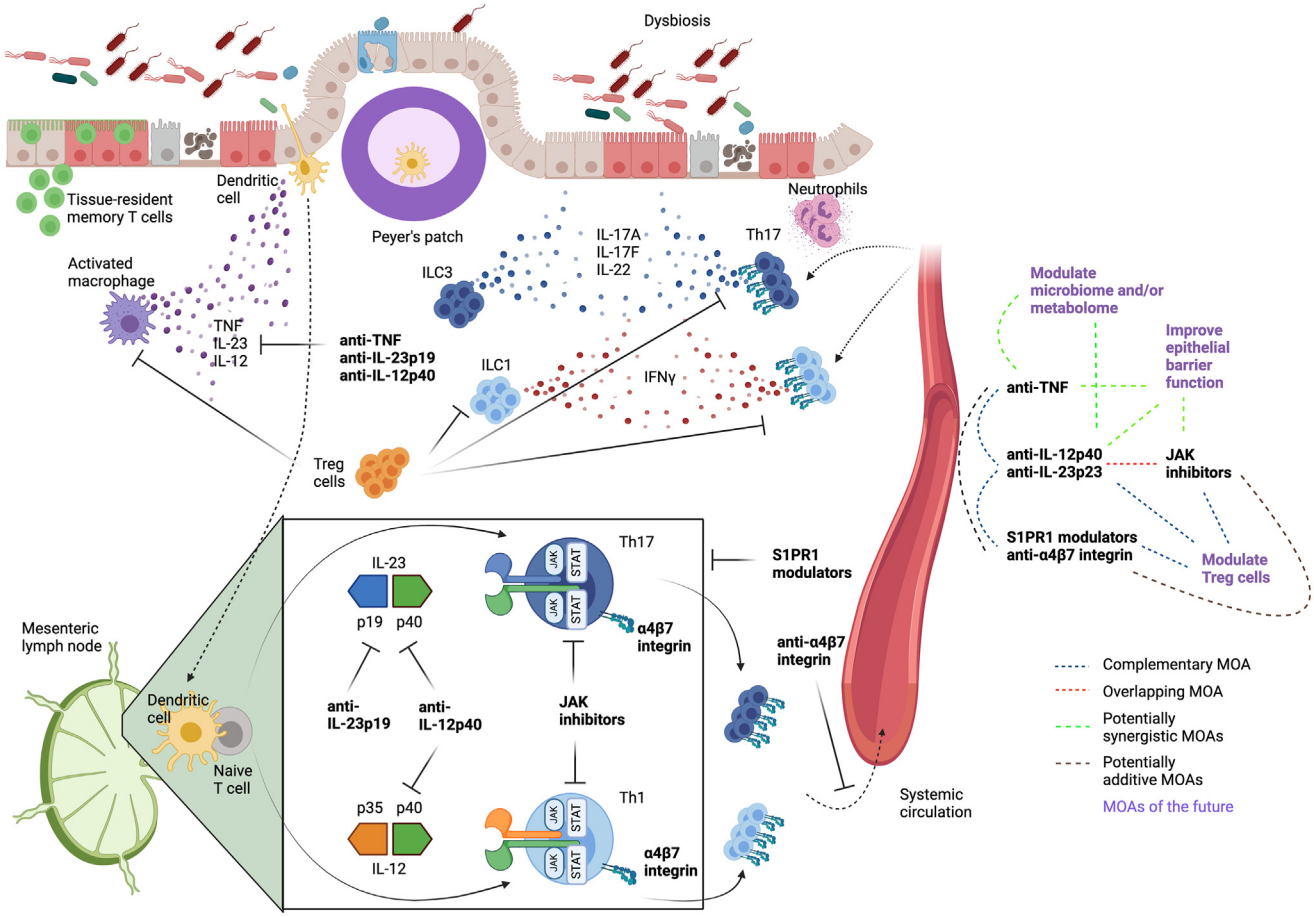

Figure 1. Mechanisms of action underlying therapies for IBD. Some alterations associated with IBD are depicted; these include microbial dysbiosis associated with increased intestinal permeability; production of inflammatory cytokines by diverse immune types; and differentiation of naïve CD4 T cells into T helper 1 (Th1) and T helper 2 (Th2) cells. Current therapeutic approaches include neutralizing cytokines that promote inflammation (anti-TNF, anti-IL-12p40, and anti-IL-23p19 antibodies) or drive the differentiation of effector $CD4^+$ T cell subsets (anti-interleukin-12p40 and anti-interleukin-23p19 antibodies); inhibiting signal transduction cascades downstream of inflammatory pathways (Janus kinase [JAK] inhibitors); or blocking lymphocyte trafficking to the intestine (anti-a4b7 integrin antibodies) or inhibiting lymph node egress (S1PR1 modulator). It should be noted that anti-IL-12p40 antibodies block both IL-12 and IL-23 signaling by virtue of their shared p40 subunit. The complementary, overlapping, and potentially synergistic mechanisms of action of current therapies and therapies of the future are indicated on the right.

leukemia inhibitor factor), interferons, and IL-10 family cytokines.[4] By contrast, filgotinib and upadacitinib preferentially target JAK1.

Drugs in the fourth group utilize various MOAs to modulate lymphocyte trafficking. Expression of a4b7 integrin enables lymphocyte trafficking to the gut mucosa by virtue of binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expressed on the endothelium of blood vessels in intestinal tissue. Vedolizumab targets $\alpha4\beta7$ integrin, which inhibits gut-selective lymphocyte trafficking, whereas natalizumab targets $\alpha4$ integrin, which prevents trafficking to the gut as well as to other tissues by blocking interactions of both $\alpha4\beta7$ and $\alpha4\beta1$ with their physiologic ligands, which include vascular cell adhesion molecule-1 (VCAM-1), MAdCAM-1, and fibronectin. Another mechanism by which lymphocyte trafficking can be modulated is through targeting sphingosine 1-phosphate receptors (S1PRs), which leads to retention of lymphocytes in lymph nodes; ozanimod, etrasimod, and VTX002 are examples of S1PR modulators.

Conceptual Frameworks for Combination Therapy

The literature is rife with various names for combinations of therapies aiming to improve treatment efficacy. Historically, combination therapy was first applied to infliximab and other biologic agents that inhibit TNF used in combination with immunosuppressive drugs such as thiopurines and methotrexate.[5] As the range of biologic agents expanded, dual biologic therapy[6] was described as the combination of 2 biologic agents with different targets. With the advent of newer targeted small molecule agents, such as JAK inhibitors and S1P1R

modulators, the possibility of "dual targeted therapy"[7,8] and "advanced combination therapy"[9] arose as a more comprehensive nomenclature encompassing 2 biologic agents, a biologic agent with a targeted small molecule agent, or 2 targeted small molecules. "Conventional therapy" is a term that is losing favor, and "advanced therapy" may not be adequately descriptive. "Advanced targeted therapy" better describes these treatments that target specific inflammatory pathways, as opposed to mesalamine and thiopurines, which do not. We favor the term "combined advanced targeted therapy" (CATT) as the most complete and accurate description of combinations of newer agents, as it is conceivable that future approaches may include combinations of 3 or even more agents.

Pharmacologic Framework

Beyond nomenclature, combination therapy may be viewed from conceptual frameworks of pharmacokinetic or pharmacodynamic synergy, and from the perspective of temporality. Examples of pharmacokinetic synergy in IBD include administration of the same active agent via 2 routes of administration, such as the combination of orally and rectally administered mesalamine.[10] More commonly, pharmacokinetic synergy encompasses 2 agents that do not offer additive benefit through complementary mechanism of action, but rather through enhancement of drug levels. The combination of infliximab with immune suppressing agents (thiopurines or methotrexate [MTX]) provides enhanced efficacy both by reducing the incidence of anti-drug antibodies as well as through an indirect effect whereby the small molecule immune suppressing agent decreases clearance of the anti-TNF antibody, thereby enhancing levels. This is substantiated by a post hoc analysis of the SONIC study demonstrating that, even early in treatment, patients in the highest quartile of trough infliximab levels were more likely to have had combination therapy, and that independent of combination therapy, infliximab trough level was associated with likelihood of response.[11]

Although combination therapy might in some cases offer pharmacokinetic advantages over monotherapy, the most substantive benefits are likely to accrue through the combined effect of drugs with different targets and distinct MOAs. Viewed through a pharmacodynamic framework, combining drugs with different MOAs might have *subadditive, additive,* or *synergistic effects* (Figure 2).[12] For example, if monotherapy with drug A yields a 20% remission rate and drug B a 40% remission rate, the results of combining drugs A and B could be said to be subadditive if it produced a 30% remission rate, additive if it demonstrated a 60% remission rate, and synergistic if it generated a 90% remission rate.[12] Similarly, one may consider the effect of combining therapies on safety and the occurrence of adverse events. For example, therapies with highly overlapping MOAs that suppress a specific arm of the immune response might produce little additional benefit while potentially increasing adverse events such as infection due to redundant and complete suppression of a critical arm of the immune response.[13] Ideally, agents addressing distinct aspects of the immune response might achieve additional therapeutic benefit without increasing risk of adverse events. However, the safety and efficacy of combinations of agents cannot be predicted entirely from each individual agent's safety profile or MOA, nor can the risk/benefit profile be anticipated solely from mechanistic studies or preclinical studies in animals. Ultimately, human studies are needed to confirm both the benefit and safety of novel combinations of drugs. Clinical trials may also need to be designed to identify the optimal dose of each component agent of the combination needed to maximize both safety and efficacy, as these may be different from the doses chosen for monotherapy.

Temporal Framework

Considerations of temporality are also relevant to the design and study of combination therapy (Figure 3). Registrational clinical trials in IBD have largely adhered to periods of induction (generally between 6 and 12 weeks) and maintenance, usually up to 48 to 52 weeks. Increasingly, this structure aligns with expectations in clinical practice, where short-term and long-term treatment targets have been adopted to guide therapy by subjective and objective response criteria. Similarly, combination therapies may be timed differently during induction or maintenance.

The most straightforward sequence is simultaneous initiation of two new therapies during the induction period (**"simultaneous induction,"** or "**co-induction**").[14] Alternatively, a second agent may be added to an initial agent ("staggered induction," or "**add-on therapy**") after some delay during induction, presumably to identify patients manifesting only partial response, and to bring the partially responding patient to full remission. Induction may also be completed as **sequential therapy (sequential induction and maintenance**; ie, a first agent to induce followed by a second agent to maintain efficacy).[14]

During the longer period of maintenance therapy, one may consider withdrawal of 1 of the 2 agents used in combination to achieve "**step-down**" therapy.[14] This paradigm is particularly sensible when the benefits of combination therapy endure beyond the time when 2 drugs are used, and safety concerns for one of the agents, or of the combination, warrant de-escalation. **Continuous combination maintenance** may also be considered when sustained combination is needed to maintain its efficacy benefit, provided that no additional safety concerns arise from long-term use of both agents.[14] Another paradigm includes **intermittent reinduction**, in which an agent with a second MOA for a short-duration is used to re-achieve control upon breakthrough of symptoms or recrudescence of inflammatory

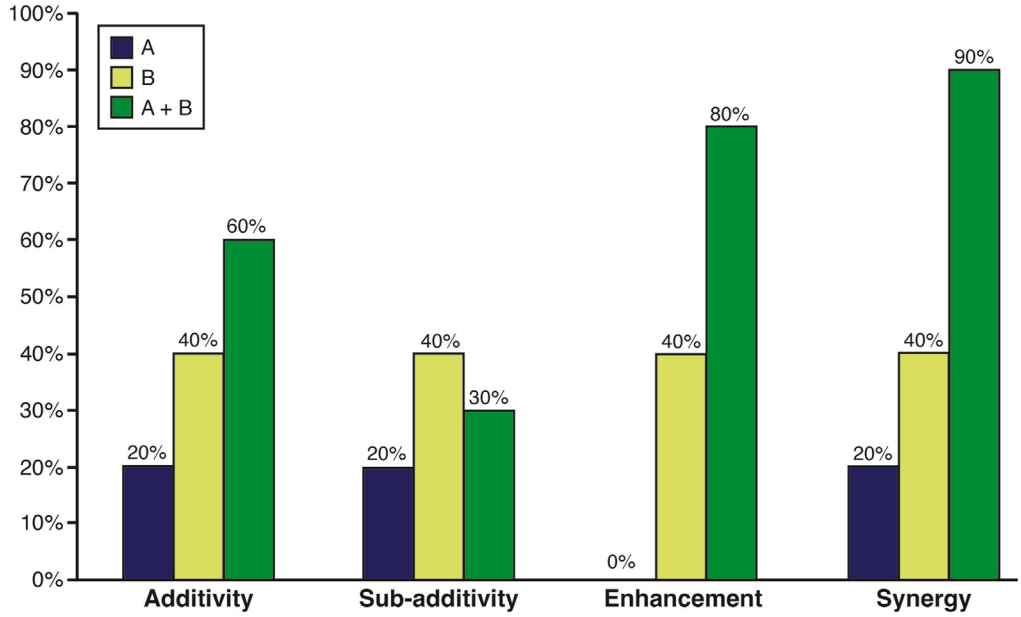

Figure 2. Describing the effects of combination therapy. The efficacy of combinations of 2 drugs may demonstrate *additivity* when the efficacy of the combination is approximately the sum of the efficacy of each therapy when used alone; *sub-additivity* when the efficacy of the combination is less than the sum of the efficacy of each therapy when used alone; *enhancement* in the situation where one drug has no efficacy when used alone, but increases the efficacy of the second therapy over what it can achieve when used alone; or *synergy* when the efficacy of the combination is greater than just the sum of the efficacies of each agent used as monotherapy.

biomarkers, or as planned cycles of therapy to maintain control.[14]

Evidence for Combination Therapy in Other Diseases

Examples of combination therapy abound in medicine. In oncology, combination chemotherapy was first employed in pediatric patients with acute lymphocytic leukemia in 1965 using a combination of methotrexate, mercaptopurine, vincristine, and prednisone.[15] Combinations of "conventional" chemotherapuetic agents have been quite successful for treatment of many malignancies, including acute lymphocytic leukemia, Hodgkin lymphoma, and testicular cancer. The rationale for combining therapies is to utilize agents with different MOAs and non-overlapping mechanisms of drug resistance to combat tumor cell heterogeneity and to reduce the risk of developing drug-resistant clones.[16] With the advent of precision medicine and targeted therapies in oncology over the past 2 decades, the number of permutations and combinations of therapies has grown exponentially. Combinations have been selected on the basis of a number of concepts, including multiple targets of a signaling pathway, inhibiting compensatory feedback regulation, enhanced synthetic lethality, collateral lethality, targeting immune cell function, and modulating the tumor microenvironment.[16]

Examples of combination therapy for treatment of locally advanced or metastatic colorectal cancer include various combinations of oxaliplatin, irinotecan, fluorouracil, and bevacizumab (antibody to vascular endothelial growth factor) for "first-line" treatment of tumors with proficient DNA mismatch repair.[17] Biomarker-driven combinations for second-line treatment of refractory cancer include the combination of a programmed cell death protein 1 (PD-1) inhibitor and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor for high microsatellite instability/deficient mismatch repair tumors, trastuzamab (monoclonal antibody to human epidermal growth factor receptor 2 [HER-2]), and a tyrosine kinase inhibitor directed against HER-2 or epidermal growth factor receptor (EGFR) for those with wild-type Kirsten rat sarcoma gene (KRAS) and overexpression of HER-2, or cetuximab (anti-BRAF) plus encorafenib (anti-BRAF kinase) for those with wildtype KRAS and BRAF V600E mutation.[18]

The development of antibiotic resistance was noted within a year of the clinical use of penicillin. Combinations of antibiotics have been increasingly employed for the treatment of bacterial and fungal infections due to the rise of drug-resistant organisms. The Centers for Disease Control and Prevention have estimated that more than 2.8 million antibiotic-resistant infections occur in the United States each year, resulting in more than 35,000 deaths annually.[19] One of the most commonly used combinations of antibiotics is amoxicillin and clavulanic acid, used to treat respiratory infections, sinusitis, and ear infections, among others. Combination antibiotic therapy is considered for multiple reasons: (1) to extend the antimicrobial spectrum; (2) to achieve a

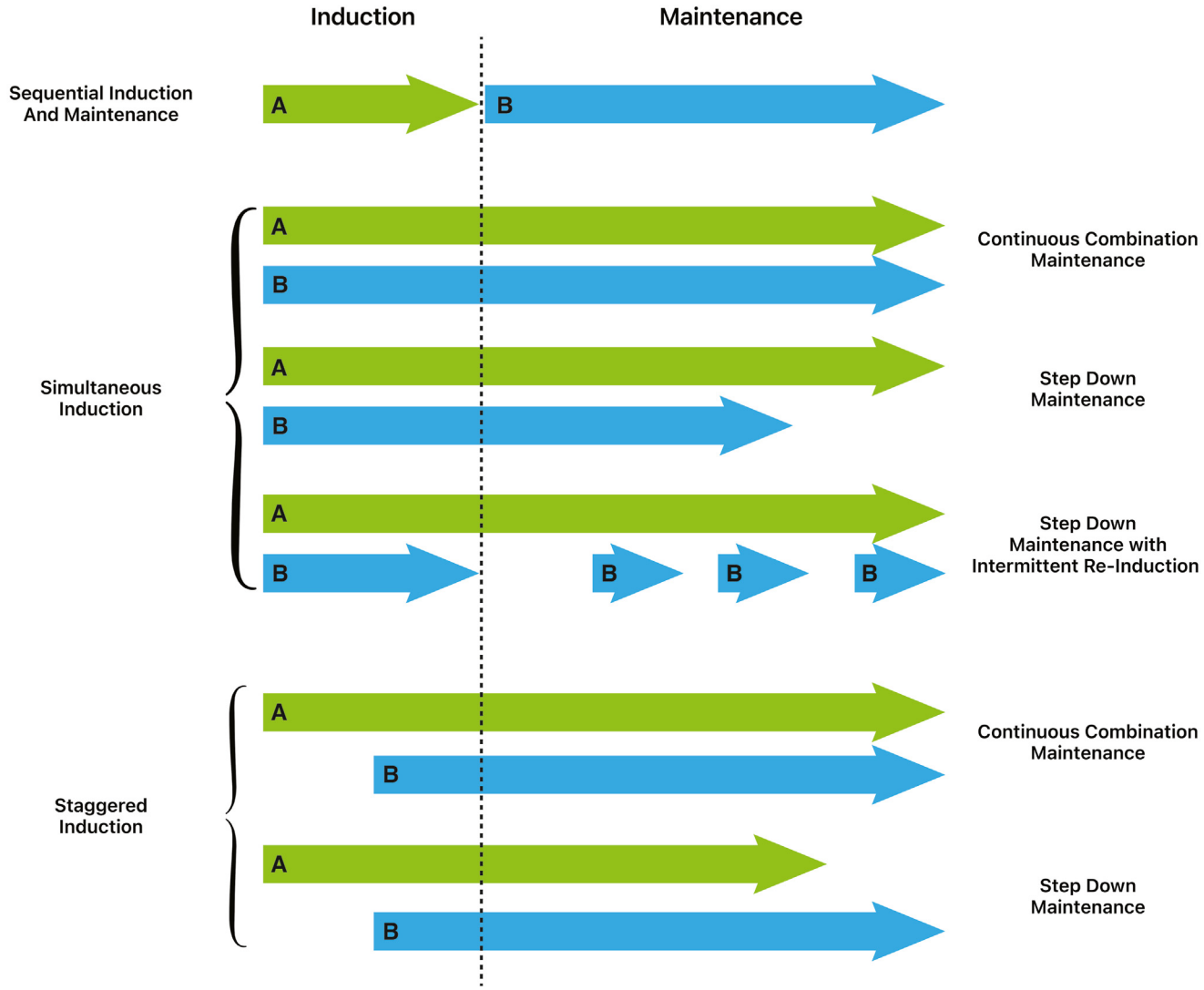

Figure 3. Temporal frameworks of combination therapy. Agents may be combined in a variety of temporal patterns to maximize both benefit and safety. Considering induction, a single drug may be used to induce remission, with intentional switch to a second agent for maintenance (sequential induction and maintenance). Simultaneous induction is conducted when 2 agents are started *de novo* at the same time, whereas maintenance may continue as ongoing combination (continuous combination), by discontinuing 1 of the 2 agents (step down), or by discontinuing an agent with periodic reintroduction of the second agent for intermittent reinduction. Finally, a second may be introduced in a delayed fashion after the first agent (staggered induction), followed by continuous combination or step down to maintain.

synergistic effect; or (3) to prevent emergence of resistance.[20] Intravenous combinations commonly employed include ampicillin and sulbactam, or piperacillin and tazobactam. Combination antibiotic therapy is frequently employed for treatment of *Pseudomonas aeruginosa* infections, active tuberculosis, *Helicobacter pylori* infections, gonorrhea, and malaria, to name just a few. Combination antibiotics are often used initially as empiric therapy (eg, in the case of community-acquired pneumonia, covering both pneumococcal and atypical pathogens)—once the pathogen has been cultured and antimicrobial resistance has been tested, often therapy can be narrowed to a single antibiotic.[20] Combination antiviral therapy has become the standard of care for definitive treatment of hepatitis C infection, achieving sustained virologic response with cure in nearly all patients while maintaining low viral drug resistance rates.[21]

Turning to other immune-mediated conditions, combination therapy is commonly used for the treatment of rheumatoid arthritis (RA) when patients have not adequately responded to conventional synthetic disease modifying antirheumatic drugs (csDMARDs).[22] The early introduction of effective therapy is thought to have had a critical impact in improving long-term outcomes in patients with RA.[23] Most randomized clinical trials of biologic DMARDs (bDMARDs) in RA have compared MTX or another csDMARD to a combination of the csDMARD with a biologic agent. The addition of MTX is not only thought to reduce the development of anti-drug antibodies to the bDMARD, but also exert its own efficacy. The benefits of combination therapy seem to be most

clear with the combination of MTX and anti-TNF agents; the addition of MTX to anti-IL-6 agents is less clear. The evidence for utility of dual bDMARD therapy in RA has been conflicting.[24] Combination of anti-TNF and anti-IL-1 was not significantly better than etanercept alone, and resulted in more serious adverse events (SAEs). Similarly, the combination of abatacept and etanercept did not confer an advantage over etanercept alone, and was associated with more SAEs. On the other hand, a small trial comparing the addition of rituximab or placebo to patients with RA on the combination of anti-TNF and MTX demonstrated increased efficacy.

Combination therapy is often used to treat psoriasis. For mild to moderate disease, topical steroids are often combined with emollients, salicylic acid, or coal tar.[25] For patients with moderate to severe psoriasis, biologics (anti-TNF, anti-IL-17, anti-IL-12/23, anti-IL-23) or systemic non-biologics or phototherapy can be used alone or in combination with topical agents.[26]

Evidence for Combination Therapy in IBD

Combination of Mesalamine Therapies

Early uses of 2 simultaneous therapies in IBD aimed to improve pharmacokinetics and drug delivery to diseased tissue. Oral aminosalicylates have clinical, endoscopic, and histologic response rates of 43%, 66%, and 52%, respectively, and these rates are not dose-dependent.[10,27,28] However, the addition of a rectal aminosalicylate to oral therapy has been shown to have higher clinical (64%), endoscopic (78%-83%), and histologic (68%-73%) response rates in ulcerative colitis.[10,27,28] This enhanced effect is presumably by delivering increased concentrations of mesalamine to the rectum and distal colon, with beneficial effects in decreasing rectal inflammation as a complement to more proximally delivered oral mesalamine.[10]

Combination of Immunosuppressants With Biologic Therapy

Subsequent uses of combined therapies utilized simultaneous immunomodulator and TNF antagonists to achieve additive efficacy with different MOAs and improved TNF-antagonist pharmacokinetics. As outlined above, the SONIC (Crohn's disease) and UC-SUCCESS (ulcerative colitis) trials showed that combination therapy with infliximab and azathioprine yielded better outcomes than monotherapy.[5,29] However, registry data have found combination TNF antagonist and thiopurine therapy to have higher rates of opportunistic infections, serious infections, and lymphoma compared with either monotherapy.[30,31]

The use of immunosuppressants with ustekinumab or vedolizumab have generally not shown additional benefit.[32] Most data show that outcomes with vedolizumab monotherapy are similar to combined therapy with vedolizumab and immunosuppressants.[33,34] One study in Crohn's disease found lower rates of treatment failure with combined vedolizumab and immunosuppressant therapy compared with monotherapy.[35] However, the weight of the evidence is weak in supporting vedolizumab/thiopurine combination therapy relative to TNF antagonists.

Combined Advanced Targeted Therapy

CATT simultaneously uses at least 2 advanced therapies (ie, biologic agents and/or advanced small molecule therapies) to obtain higher therapeutic efficacy through differing and synergistic MOAs. As advanced therapies with more favorable safety profiles (eg, vedolizumab, ustekinumab, or IL-23 antagonists) are available, these agents can be combined with a second advanced therapy with established adverse effects (eg, TNF antagonists or JAK inhibitors) while potentially preserving an acceptable safety profile. This may theoretically yield a more safe and effective option than combination thiopurine and TNF antagonist therapy. As limited data existed for this approach, clinical use of CATT has been reserved for patients with both luminal and extraintestinal disease activity, those refractory to multiple treatments, those for whom surgery would yield significant morbidity, and those with concomitant immune-mediated inflammatory disease (IMID).

Randomized Controlled Trials for Combined Advanced Targeted Therapy

In 2007, the first randomized controlled trial to analyze CATT compared simultaneous infliximab and natalizumab therapy with infliximab monotherapy and placebo in CD patients with inadequate response to infliximab. Adverse event rates were similar between natalizumab-infliximab (n = 52) and infliximab/placebo (n = 27) arms. Combined natalizumab-infliximab demonstrated numerically greater decreases in Crohn's disease activity index compared with infliximab monotherapy (−37.7 vs +3.5; $P = .08$), and more pronounced differences existed in patients with baseline elevated C-reactive protein.[36]

Recently, combination therapy of the IL-23 antagonist guselkumab and the TNF antagonist golimumab was compared with either monotherapy in a randomized controlled trial of 214 patients with moderate to severe UC (VEGA).[37] The combination arm received guselkumab and golimumab for 10 weeks, followed by subcutaneous guselkumab monotherapy every 8 weeks from week 12 to 32. Other monotherapy groups received therapy for 32 weeks. In the combination therapy arm, 83% of patients achieved clinical response, significantly higher compared with golimumab monotherapy (61%; $P =$

.003) and numerically higher than guselkumab monotherapy. Clinical remission rates in induction were also significantly higher with the combination (36.6%) compared with golimumab (22.2%; $P = .058$) or guselkumab monotherapy (21.1%; $P = .04$). At week 38, the combination arm achieved higher rates of clinical remission (44%) compared with golimumab (22%) and guselkumab monotherapy (31%). Rates of endoscopic remission, histologic remission, and complete endohistologic healing at week 38 were also higher with combination therapy compared with either monotherapy. Adverse events and serious infections until week 50 were similar between groups. Further phase IIb trials are underway for both CD and UC to assess this strategy.

Observational Data for Combined Advanced Targeted Therapy

Observational data for CATT exist in patients with treatment-refractory IBD or those with concomitant IMIDs.[7,38–40] For example, in a cohort of 24 CATT trials described by Yang et al, 91% had prior IBD-related surgery, 50% had perianal fistulae, and all patients had failed multiple biologic agents (median of 4).[39] Based on both observational and randomized controlled trial data, meta-analyses published in 2021 identified published data on 279 patients receiving CATT.[41] These included patients receiving concomitant vedolizumab with TNF antagonists (48%), vedolizumab with ustekinumab (19%), and TNF antagonists with ustekinumab (7%). Most patients previously failed biologic therapy (61%), and 47% had already undergone at least one IBD-related surgery. Over a 32-week median follow-up time, pooled clinical and endoscopic remission rates were 58.8% (95% confidence interval [CI], 42%-74.5%) and 34.3% (95% CI, 23.5%-46.1%), respectively. The pooled SAE, infection and malignancy rates were 6.5% (95% CI, 2.1%-13.1%), 19.7% (95% CI, 13.3%-27%), and 1.6% (95% CI, 0.3%-3.6%), respectively.

Another meta-analysis used patient-level data to specify outcomes for each CATT combination in 266 patients.[42] In patients receiving simultaneous TNF antagonist and ustekinumab, the clinical and endoscopic (or radiologic) remission rates were 76.5% and 35.9%, respectively. In patients receiving combined vedolizumab and TNF antagonists, the clinical and endoscopic (or radiologic) remission rates were 55.1% and 18%, respectively. Combined tofacitinib and vedolizumab yielded a 47.8% clinical remission rate and a 24.6% endoscopic (or radiologic) remission rate. Simultaneous use of vedolizumab and ustekinumab demonstrated a 47% clinical remission rate and a 25.6% endoscopic (or radiologic) remission rate. Pooled SAE rates were 12.3% for combined vedolizumab and ustekinumab, 9.6% for TNF antagonist/vedolizumab, 0% for TNF antagonist/ustekinumab, and 1.0% for tofacitinib/vedolizumab.

Most recently, the EXPLORER trial was an open-label observational study in 55 biologic-naïve patients with moderate- to high-risk CD.[43] Triple combination therapy with vedolizumab, adalimumab, and MTX for 26 weeks showed clinical and endoscopic remission rates of 55% and 35%, respectively. Serious adverse events were observed in 6 patients.

Current Applications for Combined Advanced Targeted Therapy

CATT is currently used in patients who are refractory to multiple therapies or in scenarios where concurrent extraintestinal manifestations or IMIDs make this approach preferable.

General CATT Approach

In patients with multiple treatment failures, rational combination entails a detailed understanding of prior medication failures, including: (1) whether an initial clinical response was obtained; (2) adverse drug-related effects (especially SAEs such as anaphylaxis and infections); (3) presence of penetrating disease or perianal fistulae; (4) presence of extra-intestinal symptoms and/or IMIDs; (5) criteria for determining prior treatment failure (ie, endoscopic documentation, treatment intolerance, possible confounders leading to IBD symptom mimics); and (6) drug pharmacokinetics and dosing (whether performed at time of treatment failure, presence of anti-drug antibodies, attempts to overcome either low drug concentrations or anti-drug antibodies). In a patient requiring CATT, therapies that have previously had primary non-response or associated with an SAE are typically not used in the combination.

Absent any special considerations, an advanced therapy with favorable safety profile (eg, vedolizumab, ustekinumab, or IL-23 antagonists) may be combined with each other or a second advanced therapy with established adverse effects (ie, TNF antagonists or JAK inhibitors). Using 2 agents with established adverse effects would likely be unsafe. The combination of a TNF antagonist and IL-23 antagonist as induction and maintenance therapy is a rational combination given complementary safety profiles and data showing that patients who do not respond to TNF antagonists have upregulated mucosal IL-23.[44,45] Alternatively, use of an agent with a favorable safety profile (eg, vedolizumab, ustekinumab, IL-23 antagonist) combined with a JAK inhibitor may be used in either step-down or as intermittent combination therapy.

De-escalation by removing a single therapy in CATT and timing of de-escalation is an individualized decision. Long-term data on safety of CATT are lacking. In patients without response to CATT, surgery is often needed. In patients with significant response or remission with CATT, personalized discussions between providers and

patients are needed to jointly decide whether trial withdrawal of one therapy in the combination would be attempted. There are lack of data on the optimal de-escalation strategy, and it will be important to determine (1) whether dose reduction of an agent with known adverse events would be attempted prior to complete withdrawal of the agent, (2) whether dose optimization of the biologic desired for monotherapy is needed prior to withdrawal of the second agent, and (3) optimal strategy for potential recurrence of disease after withdrawal of a second agent in patients in whom remission was achieved.

Special Considerations

In patients with fistulae, a TNF antagonist would likely be a useful agent in the combination. Patients with psoriatic diseases would benefit from an IL-23 antagonist, IL-12/23 antagonist, TNF antagonist, or JAK inhibitor. Patients with hidradenitis suppurativa, RA, or ankylosing spondylitis would benefit from TNF antagonists or upadacitinib (Table 1). Those with pyoderma gangrenosum would likely benefit from a TNF antagonist. In patients with multiple sclerosis, an S1P antagonist or natalizumab would have utility.

Family planning is also an important consideration: no data exist on the safety of CATT in pregnancy, and it should currently be avoided in those attempting to conceive actively. In those wishing to conceive, CATT may be an option if significant response or remission can be achieved with CATT for 6 to 12 months, without relapse after de-escalation of one of the therapies (ie, a single therapy that is well-studied in pregnancy is used to maintain remission in pregnancy). As more data emerge, it is possible that selected combinations may be safe in pregnancy. In general, biologics are all considered safe in pregnancy, and data are likely to show biologics currently approved in IBD will be safe in combination. In addition, data show biologics, azathioprine, or their combination do not increase the risk of adverse pregnancy-related outcomes.[46] Small molecule advanced targeted therapies have known adverse safety effects in pregnancy and should be avoided in this context.

The Future of Combination Therapy in IBD

New Mechanisms of Action

Combination therapies with MOAs distinct from those of currently approved drugs may have the greatest likelihood of breaking through the therapeutic ceiling currently faced with monotherapies. Examples of distinct MOAs include promoting anti-inflammatory mechanisms such as regulatory T (Treg) cells, maintaining barrier integrity and promoting mucosal healing, and modulating the microbiome.

Changes in the composition of microbial communities, such as reductions in the total number, diversity, and richness of microbial species, has been shown to occur in IBD, raising the possibility that interventions that target the microbiome may be therapeutically useful.[47] However, the efficacy of fecal microbiota transplant (FMT) has been variable across clinical trials, likely owing to differences in trial design, disease heterogeneity, and a lack of clarity as to the specific component of donor feces that is responsible for a possible beneficial effect.[48] Other untargeted approaches to modulate the microbiome include prebiotic carbohydrates, a substrate for bacterial growth, which may stimulate the growth and activity beneficial members of the gut microbiota, and probiotics containing different strains or species of microorganisms.[49] Targeted approaches of the future may include transfer of defined communities of microbes that induce

Table 1. Special Considerations in CATT

	Agent to consider for inclusion in combination				
Disease	TNF antagonist	JAK inhibitor	Anti-integrin	IL23 or IL12/23 antagonist	S1P inhibitor
Fistulizing Crohn's disease	Yes	Possible	Possible	Possible	–
Atopic dermatitis	–	Yes	–	–	–
Hidradenitis suppurativa	Yes	–	–	–	–
Pyoderma gangrenosum	Yes	–	–	–	–
Rheumatoid arthritis	Yes	Yes	–	–	–
Psoriatic diseases	Yes	Yes	–	Yes	–
Ankylosing spondylitis	Yes	Yes	–	–	–
Uveitis	Yes	–	–	–	–
Multiple sclerosis	–	–	–	–	Yes

CATT, Combined advanced targeted therapies; IL, interleukin; JAK, Janus kinase; TNF, tumor necrosis factor.

anti-inflammatory immune responses, bio-engineered commensals expressing molecules with beneficial effects, delivery of tailored drugs that target specific microbial-synthesized metabolites, and transfer of bacteriophages to target dysbiotic components of the microbiome.[49]

A complementary approach to neutralizing inflammatory cytokines would be to increase the efficacy of anti-inflammatory factors, such as the cytokines IL-10 and transforming growth factor (TGF)-β, either by direct administration of these factors or by increasing the function of cells, such as Treg cells,[50] that produce these factors. Possible strategies include transfer of *ex vivo* expanded Treg cells[51]; administration of low dose IL-2, which preferentially expands Treg cells compared with inflammatory T cells owing to their higher expression of the alpha chain of the IL-2 receptor (IL-2Rα, CD25)[52]; and the use of IL-2 mimetics that selectively target Treg cells.[53]

Mucosal barrier dysfunction is a consequence of IBD, and barrier integrity defects include increased permeability, mucosal erosion, reduced mucus layer, impaired production of defensins, and decreased numbers of goblet cells.[54] For example, targeting lipid mediators, such as resolvin E1, which restores mucosal homeostasis, may improve barrier integrity.[55,56] Inhibition of plasminogen activator inhibitor-1, a serine protease inhibitor of fibrinolysis involved in the coagulation cascade, reduces colitis and crypt hyperplasia, potentially by reducing proliferation of wound-associated epithelial cells.[57] Divertin is a rationally designed inhibitor of myosin light chain kinase, a central regulator of intestinal epithelial tight junctions and putative mediator of TNF-induced barrier dysfunction.[58] Lastly, IL-22 controls multiple aspects of epithelial barrier function and may be a promising therapeutic target to improve epithelial homeostasis in IBD.[59]

Future Evolution of Combined Advanced Targeted Therapy in IBD

Loss of response is a major issue in patients receiving advanced therapies, and efficacy diminishes with each additional biologic therapy attempted. Using therapy that blocks 2 mechanisms of action synergistically may address secondary loss of response by inhibiting escape of inflammatory immune cells from selection pressures of a single therapy. Future data may demonstrate superior efficacy or durability of response of CATT compared with monotherapy, with a preserved safety profile. As using a highly effective agent early yields improved outcomes,[60] positioning of CATT may become an earlier (or first-line) therapy. Although precision biomarker-based approaches are being attempted, highly efficacious therapy may negate the need for this approach. Ideally, the evolution of IBD therapy would be analogous to hepatitis C therapy: CATT may break through therapeutic ceilings, negating the need to sub-stratify patients with IBD for treatment selection, instead using one highly efficacious treatment combination to induce deep remission in nearly all patients with IBD.

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The Future of Clinical Trials in Inflammatory Bowel Disease

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The medical management of inflammatory bowel disease (IBD) has been transformed over the past few decades by the approval of multiple classes of advanced therapies and the integration of more targeted treatment strategies for Crohn's disease and ulcerative colitis. These changes have been driven by an increasing number of pivotal randomized controlled trials, which have grown in size and complexity over time. Several landmark studies that are anticipated to change current IBD management paradigms have recently been completed or are on-going, including the first head-to-head biologic trials, advanced combination treatment trials, therapeutic strategy and treatment target trials, and multiple phase 3 registrational programs of novel compounds. Despite these advances, the future of IBD trials also faces major challenges with respect to cost, feasibility, and recruitment. Accordingly, innovative methods for early and late phase randomized controlled trials must be adopted. In this review, we provide a comprehensive overview of the evolution of modern IBD trials, discuss methods for improving trial efficiency in early and late phase development, and provide insights into the interpretation and implications of these data for clinical care.

Keywords: Controlled; Crohn's Disease; Randomized; Trials; Ulcerative Colitis.

The past 2 decades have witnessed major advancements in the management of inflammatory bowel disease (IBD). This has been highlighted by the approval of several classes of advanced biologic and oral small molecule therapies for moderately-to-severely active Crohn's disease (CD) and ulcerative colitis (UC) in addition to an increasing emphasis on (1) early disease recognition and treatment initiation[1]; (2) comprehensive disease assessment and monitoring capturing patient-reported outcomes (PROs) and objective biomarker, endoscopic, radiographic, and histologic disease measures[2]; and (3) adoption of treat-to-target therapeutic paradigms that focus on long-term mucosal healing, normalization of quality of life, and prevention of bowel damage and disability.[3] Much of this progress has been driven by rigorously executed randomized controlled trials (RCTs), including both premarketing registrational studies to demonstrate the efficacy and safety of novel therapies and postmarketing, large-scale therapeutic strategy trials that have advanced the thinking and ambitions for the potential of disease modification and positively changing the otherwise progressive and debilitating natural history of IBD.[4]

The complexity, scope, and investment of monetary, operational, and patient resources in clinical trials in IBD have increased over time. Trials of advanced therapies in IBD have evolved from isolated short-term induction trials to open-label induction with randomized maintenance studies, and subsequently to integrated "treat-through" combined induction and maintenance studies and induction and responder rerandomization trials with withdrawal of some patients to maintenance placebo.[5] Although these different designs has allowed greater possibilities for the types of clinical questions that can be answered in RCTs, tremendous challenges also exist.[6] For example, despite rising prevalence rates of IBD, enrolment in clinical trials has decreased and now averages <0.2 patients per site per month and even less in North America.[7] Up to half of trials fail to meet recruitment timelines, 20% of development programs are prematurely terminated, and the duration and cost of running large-scale studies has increased exponentially.[6] Second, although there are now more medical options than ever to treat patients with IBD, the "therapeutic ceiling" constraining long-term remission rates has yet to be broken.[8] Third, there has been an explosion in the generation of "real-world" data that often includes a broader range of participants compared with RCTs, and can evaluate different components of treatment effectiveness, assess long-term treatment safety, and inform treatment decisions that are not directly answered in controlled studies.[9] However, data collected from observational studies

Abbreviations used in this paper: **CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IBD, inflammatory bowel disease; IL, interleukin; PK, pharmacokinetic; POC, proof-of-concept; PROs, patient-reported outcomes; RCT, randomized controlled trials; UC, ulcerative colitis.**

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are limited by the inability to control for unmeasured confounders, bias with respect to patient selection, and potential inaccuracies in outcome ascertainment. Therefore, designing practical, recruitable, and generalizable trials that target creative strategies for improving patient- and population-level rates of remission remains a priority for the next generation of IBD RCTs.

In this review, we summarize important advancements in the conceptualization, design, and conduct of early and late-phase trials, focusing on how IBD RCTs have changed over time, challenges in current trials (Table 1) and where opportunities exist to advance the standard of research and clinical care (Table 2).

Innovations in Early Phase Trials

In early drug development, the primary goals are to evaluate safety and tolerability, establish proof-of-concept (POC) for potential mechanistic efficacy, assess pharmacokinetic (PK) and pharmacodynamic dose-response relationships, and determine progression to phase II and ultimately a registrational phase III program. Conventionally, this has consisted of single and multiple ascending dose PK and safety studies in healthy volunteers, followed by POC and parallel or multiple group dose-finding trials that have assessed clinical outcomes using the Mayo Clinic Score in UC or the Crohn's Disease Activity Index (CDAI) in CD.[10,11] Some programs have incorporated cohorts of patients with IBD at this single and multiple ascending dose phase to obtain some very preliminary signals of safety and drug target engagement. However, this "traditional" model of drug development is inefficient and often requires >150 participants randomized to multiple groups, which is infeasible to rapidly recruit without coordinated efforts at site activation and aggressive screening on a global scale.[12] Accordingly, several considerations for more efficient early phase drug development have been proposed.

Exposure-Driven Pharmacokinetics

Historically, population-based PK modelling has been used to refine multiple fixed dosing regimens that are tested in phase 2 to assess for potential dose-response relationships. However, there is considerable intra-individual and interindividual variability in PK, particularly of biologic therapies, based on such factors as body weight, disease activity, albumin, and drug-related immunogenicity.[13–15] Recognizing that systemic drug levels may be correlated with clinical response, dosing in early phase trials based on measured treatment exposure may be more efficient than fixed dosing, to minimize the risk of primary nonresponse because of suboptimal PK. This approach was used in the phase 2 AMAC mirikizumab trial in patients with moderately-to-severely active UC.[16] Eligible patients were randomized to placebo, 600-mg mirikizumab fixed-dose, or 50-mg and 200-mg mirikizumab exposure-based dosing administered at Weeks 0, 4, and 8 (allowing for up to 12-fold dose escalation at Weeks 4 and 8). Although clinical response and remission rates did not vary by dose adjustment, investigators were able to increase serum mirikizumab concentrations among patients with the lowest therapeutic exposure after the first 2 doses, exclude an obvious exposure-dependent response, and identify that the lower responses observed in the 600-mg treatment arm were not caused by inadequate exposure. Subsequently, mirikizumab 300 mg was demonstrated to be significantly superior than placebo for inducing clinical remission at Week 12 in the LUCENT-1 phase 3 trial.[17]

Target Engagement for Proof-of-Concept and Measuring More Statistically Efficient Outcomes

Clinical response and remission using the CDAI or Mayo Clinic Score have historically been used to assess efficacy in phase 2 trials. However, these outcomes are

Table 1. Challenges with Current IBD Clinical Trials

Challenges in trial screening	Low rates of trial recruitment and site engagement Lack of precision-medicine or biomarker-targeted screening approaches Poor representation of ethnically and racially diverse patients and disadvantaged patient populations
Challenges in trial conduct	Inefficient trial designs and drug development paradigms, requiring large number of patients Highly stringent but poorly generalizable inclusion and exclusion criteria Complex trial procedures and schedules of events, that inconsistently reflect clinical care Lacking patient-centric study procedures, including randomization to placebo and prolonged drug washout periods
Challenges in trial interpretation	Heterogeneously defined outcome measures Inability to detect early target engagement and use of statistically inefficient end point measures Large numbers of end points, often of uncertain clinical meaningfulness Poor correlation between symptom-based end points and objective disease measures

IBD, inflammatory bowel disease.

Table 2. Opportunities to Improve Future IBD Clinical Trials

Innovations in early phase trials	Dosing based on exposure-driven pharmacokinetics to minimize risk of underdosing or overdosing Measurement of target engagement to confirm proof-of-concept Using more statistically efficient continuous outcome measures to make go/no-go trial decisions Minimize randomization to placebo using Bayesian frameworks or master trial protocols
Innovations in late phase trials	Using integrated phase 2 and phase 3 programs to maximize efficiency Eliminating the artificial dichotomy between induction and maintenance treatment periods Qualifying patients on objective disease markers Expanding enrolment to include historically marginalized and minority patient populations Implementing efficient strategies to facilitate screening (eg, always-on endoscopy recording, social media driven patient-centered trial recruitment) Designing trials to assess patients with specific IBD phenotypes (eg, pouchitis, perianal CD, proctitis) Measuring validated, reliable, and responsive patient-reported and endoscopic outcomes Assessing head-to-head active treatment comparisons and therapeutic treatment strategies, such as advanced combination therapy

CD, Crohn's disease; IBD, inflammatory bowel disease.

inefficient: clinical assessments are only indirect measures of pharmacodynamic effects, they may not be sufficiently sensitive to capture early treatment response, and subsequent power calculations to inform phase 3 trials are often based on imprecise estimates.[18] Furthermore, dichotomization of these outcomes loses important information. Novel advancements in translational techniques, such as single-cell RNA sequencing and spatial transcriptomics, now allow better direct measurement of target engagement to confirm POC, either in peripheral blood or intestinal tissue.[19] This allows potentially greater confidence in making early go/no-go decisions regarding trial progression using detection of molecular changes and confirmation of biologic efficacy. One such example is the phase 2a FUTURE trial, a 12-week open-label prospective study including only 16 patients with active UC and CD, treated with olamkicept (a sgp130Fc decoy protein that blocks interleukin [IL]-6 signaling).[20] This POC trial demonstrated efficacy using target inhibition of phosphorylated signal transduction and activation of transcription (STAT)-3 and transcriptional changes from intestinal biopsies. An important consideration from this study is whether the demonstrated inhibition of STAT3 phosphorylation with olamkicept is simply a surrogate measure of biologically reduced inflammation, with downregulation of multiple STAT3-dependent gene transcripts. This illustrative example highlights the difficulty in finding true markers of target engagement.

Although dichotomizing treatment end points into binary response versus nonresponse is clinically intuitive, this approach may not be sensitive for detecting change after treatment. In the worst-case scenario, using a binary outcome in early phase development that is insensitive for responsiveness can lead to the erroneous abandonment of potentially effective medications at the POC stage. One alternative to mitigate this risk is to use a more sensitive composite or continuous end point to enhance signal detection for treatment efficacy. For example, the UC-100 score was developed and validated for this purpose.[21] This is a 100-point continuous measure that includes weighted assessment of stool frequency, histologic activity measured using the Robarts Histopathology Index, and the Mayo Clinic endoscopy subscore. In a post hoc analysis of the ustekinumab UNIFI trial, using the UC-100 instead of the Mayo Clinic Score would allow a similarly powered trial with a 30% reduction in total sample size.[22]

Minimizing Randomization to Placebo

In earlier phase trials, the possibility of being randomized to placebo is often an important deterrent for participants, and indeed, it is debatable whether it remains ethical to randomize patients to placebo given the availability of other effective and safe therapeutic options.[23] Different proposals for minimizing the number of participants randomized to placebo have been considered. One solution is to conduct an open-label single-arm trial using an objective, centrally evaluated and blinded end point: this allows all participants to receive active treatment yet preserves the validity of efficacy assessments. An example of this design is the phase 2a single-arm TUSCANY trial, where Danese et al[24] evaluated the efficacy and safety of PF-06480605, a monoclonal antibody targeting tumor necrosis factor-like ligand 1 (TL1A). The primary end point of this trial was centrally read endoscopic improvement at Week 14. The trial was conducted using a Simon's 2-stage design, initially assessing for futility in the first 12 participants, and then testing the proportion of participants achieving endoscopic improvement against a historical placebo response rate of $\leq$6% (observed in tumor necrosis factor

antagonist experienced participants in the phase 3 OCTAVE tofacitinib trials).

Although Danese et al[24] used a frequentist framework for testing a null hypothesis using observed data from the TUSCANY study, an alternative solution for minimizing patients randomized to placebo is to conduct a Bayesian trial. Bayesian designs summarize previous observations in the literature about an outcome to estimate a prior distribution, which is then updated using data collected from the trial to a posterior distribution from which probabilities with credible intervals can be derived for making comparative inference.[25] Bayesian trials are potentially viable in IBD because a large body of evidence synthesizing clinical, endoscopic, and histologic placebo responses in CD and UC using both trial- and individual patient-level data has been conducted to inform prior estimates.[26–29] Second, both trial- and patient-level factors associated with placebo responses have been evaluated.[30,31] The earliest example of a Bayesian RCT in IBD evaluated secukinumab, a monoclonal antibody targeting IL17A, which demonstrated harm after enrolling only 59 participants.[32] More recently, the EXPLORER trial was a single arm, open-label study, which treated 55 biologic-naive patients with CD with triple combination vedolizumab, adalimumab, and methotrexate.[33] A Bayesian prior was developed from past vedolizumab and adalimumab studies; it was estimated that Week 26 centrally read endoscopic remission on triple combination therapy was more likely compared with placebo ($\geq$99.99%), vedolizumab ($\geq$86.26%), or adalimumab monotherapy ($\geq$71.35%). Finally, Bayesian approaches are typically better suited to be combined with adaptive trial designs, particularly those that combine multiple phases or have adaptive randomization allocation ratios that favor active treatment.[34]

Although this improves trial efficiency, it should be cautioned that adaptive Bayesian trials may be logistically challenging to design and require complex analytic methods to control the risk of type 1 error. Furthermore, although this methodology is well established, regulatory authorities tend to be very conservative in their recommendations when such designs are proposed to mitigate pitfalls that can occur with using historical estimations of placebo response. For example, the lack of blinding may influence the estimation of nonobjective end points, historical controls must adequately mimic the study population although it is difficult to ascertain unmeasured sources of confounding and patient characteristics may shift over time, and finally, very large and convincing treatment effects must be anticipated to be confident in the findings compared with historical placebo groups.[35]

A third potential solution for minimizing the number of participants randomized to placebo is to adopt a master trial protocol, which involves a single, overarching protocol to answer multiple questions. An umbrella trial that evaluates multiple treatments in a single disease state can share a common comparator group and skew the randomization toward heavily favoring active treatment. For example, the phase 2b VIBRATO trial simultaneously evaluated the efficacy and safety of ritlecitinib and brepocitinib in moderately-to-severely active UC.[36] Both agents were compared with a shared placebo arm and fewer than 10% of participants (25/319) were randomized to placebo. In contrast, a basket trial evaluates the same drug for multiple diseases under the same protocol. RELIEVE UCCD is an example of a phase 2b basket trial evaluating the efficacy, safety, and tolerability of anti-TL1A in both patients with UC and CD, incorporating a common protocol with the goal of improved efficiency for recruitment for both indications without the need for separate trials.[37] Finally, a platform trial design can be considered: platform trials are "open-ended" designs, that allow new interventions to be added so that multiple therapies can be simultaneously or sequentially evaluated, with no prespecified trial end date. The ongoing MACARONI-23 platform trial is evaluating pediatric patients with moderate-to-severe CD, treated with guselkumab or mirikizumab, and with the anticipation of additional treatment arms being added in the future.[38]

Innovations in Late Phase Trials

Over the past 3 decades, there has been substantial evolution in the design of late phase registrational studies in IBD, from isolated short-term induction trials to open-label induction with randomized maintenance studies, to "treat-through" induction and maintenance, to integrated induction and responder rerandomization designs. These different configurations answer fundamentally different clinical questions, with each having unique advantages and disadvantages with respect to feasibility of recruitment, risk of drop-out, generalizability to routine care, and interpretation of treatment efficacy and safety.[5] Although recently, the induction and rerandomization of responders (also termed "induction followed by randomized withdrawal maintenance" when only induction responders to active treatment are rerandomized) has been a preferred design: it can be argued that this most closely mimics real world practice where primary nonresponders are continued on long-term treatment. However, there have been multiple recent variations in phase 3 designs and advancements in how late phase trials are conducted.

Innovations in Late Phase Trial Configurations

Historically, there has been a dichotomy between induction and maintenance periods for IBD trials. In earlier induction studies, outcomes were often measured 4–8 weeks after randomization, yet this is inconsistent with the observation that in clinical practice, many patients take longer to respond. Accordingly, recent phase

3 trials have measured induction outcomes later at 12–16 weeks, and often included an "extended induction" period to try and capture delayed responses. For example, in the phase 3 ADVANCE and MOTIVATE trials that evaluated the efficacy and safety of risankizumab, induction nonresponders at Week 12 were eligible to receive an additional 12 weeks of open-label therapy.[39] More than 50% of induction nonresponders experienced clinical improvement and one-third had an endoscopic response to extended treatment with risankizumab, supporting the clinical message that risankizumab could be continued for 6 months after induction to capture early delayed responders.

The concept of extending induction highlights the rather artificial separation between induction and maintenance periods, which has not been commonly adopted in trials for other chronic inflammatory diseases, such as rheumatoid arthritis. Some limitations of using this dichotomy in induction responder rerandomization designs should be noted: (1) maintenance efficacy is only reflective of induction responders and the characteristics of this subgroup may be different than those randomized at baseline; (2) "carry-over" effects after induction can influence the interpretation of data from the withdrawal of therapy arm in maintenance, particularly for treatments with long half-lives or prolonged pharmacodynamic effects[40]; and (3) rerandomization is inherently inefficient because induction trials are must be overpowered to have sufficient responders feed the maintenance study. Given these limitations, there has been increasing interest in returning to "treat-through" designs. For instance, the etrasimod ELEVATE52 trial included a 12-week induction and 40-week maintenance period; however, all participants continued their randomized treatment assignment from baseline.[41] This treat-through registrational trial was conducted with a relatively smaller sample size (n = 433). It is noteworthy that clinical remission (25.4% in all randomized patients) was numerically lower than typically observed in rerandomization studies, yet when only Week 12 responders were considered, 31.9% were in clinical remission at Week 52.[42] Treat-through studies are also at greater risk for differential drop-out between groups as the trial progresses: in ELEVATE52, 54% of participants receiving placebo compared with 36% of participants receiving etrasimod discontinued before Week 52. Although this was primarily attributed to disease worsening, it is important that participants discontinuing early have objective evidence of active disease and that the interpretation of adverse event rates accounts for differences in treatment/placebo exposure.[43]

Traditionally, phase 3 programs in IBD have consisted of 2 induction studies confirming efficacy. To maximize efficiency, some sponsors have used an integrated phase 2b/phase 3 approach that combines dose-ranging and dose-confirmation and rolling over participants directly into a phase 3 confirmatory maintenance trial,[44,45] although this requires coordinated operational efforts with standardized trial procedures, homogeneity of eligibility and outcome response criteria, interim readouts of phase 2b results, and sufficient availability of drug supply. Notably, the Food and Drug Administration does support a pathway to drug approval using a single, adequately powered, well-controlled efficacy trial that demonstrates highly significant efficacy ($P < .001$ or better).[46] Although a single induction trial simplifies monitoring and interpretation, it is also an obvious risk for drug development, particularly if statistical significance at $P < .05$ but not a more stringent threshold is achieved. The single trial configuration was used in the LUCENT-1 phase 3 mirikizumab study, which consisted of a single placebo-controlled induction RCT and analyzed with a familywise error of 0.00125 to test the primary and major secondary end points, reporting multiplicity-controlled outcomes with 99.875% confidence intervals.

A last recent change in the configuration of IBD trials to consider involves the management of concomitant medications, which are typically strictly controlled to avoid confounding interpretation of efficacy. Historically, corticosteroids were allowable, yet the dosing was fixed during the screening and induction. This clearly does not reflect routine care, where patients and providers are keen to taper and withdraw steroids quickly. The U-EXCEL and U-EXCEED upadacitinib CD trials were the first registrational program to include corticosteroid tapering during induction (following a protocolized taper beginning at Week 4) and reporting of corticosteroid-free end points at Week 12.[47] In most maintenance studies, corticosteroid-free remission is lower than the total trial population by approximately 25%, whereas in the U-EXCEL (Δ27.7% vs Δ20.8%) and U-EXCEED (Δ22.5% vs Δ17.9%), a greater separation between upadacitinib and placebo was observed for corticosteroid-free compared with all-comer remission at Week 12. This suggests that early corticosteroid tapering may be an effective mechanism for differentiating efficacious and rapidly acting therapies from placebo.

Defining Phase 3 Trial Populations

A critical advancement in recent phase 3 trials in IBD is the requirement to qualify all patients at baseline using endoscopy.[48] This was driven by the observation that historical placebo rates when patients were enrolled using symptoms alone was high, symptoms are poorly correlated with objective disease measures, and several promising treatments failed to demonstrate efficacy because of high placebo responses.[49,50] The requirement for baseline populations to have a minimum threshold of endoscopic activity (usually Mayo Clinic endoscopy subscore $\geq$2 in UC and Simple Endoscopic Score for CD $\geq$6 or $\geq$4 for isolated ileal disease), confirmed by centrally read and blinded experts, has markedly reduced placebo response rates in both UC and CD and has

ensured that eligible populations have active inflammation that can respond to effective therapy.[29]

Other important changes in trial populations have occurred over time. First, historically very low rates of ethnic minorities and underrepresented populations have been represented in IBD trials. This is despite increasing incidence of IBD in racially diverse patients around the world, and minority populations being disproportionately burdened by disparately negative health indicators of chronic disease, with differences in outcomes associated with systemic and structural racism, implicit treatment biases, and socioeconomic disadvantages.[51] In recent years, there has been an increasing push to be more broadly inclusive in IBD trials, with increasing enrolment from Eastern Europe, South America, and the Asia-Pacific.[52] Furthermore, integration of methods for conducting "decentralized" trials can also improve the availability of RCTs to participants in rural and nontertiary care referral centers. Second, earlier IBD trials often restricted patients based on prior treatment failure because they are less likely to respond; however, as more patients are exposed to advanced therapies as part of routine care, trial sponsors have increasingly broadened their inclusion criteria to include patients with previous advanced treatment exposure, and inclusion of traditionally excluded subtypes, such as proctitis. Interpretation of subgroup analyses based on prior biologic or small molecule therapy failure should consider that these populations are highly heterogeneous, and the underlying pathophysiology of primary compared with secondary nonresponse or patients with intolerance may be different.[53] Third, there is increasing interest in enrolling populations of patients with IBD with specific phenotypes that have been conventionally excluded from study participation. For instance, patients with chronic pouchitis after ileal pouch–anal anastomosis for UC were recently evaluated in the phase 4 EARNEST trial, which demonstrated that vedolizumab was significantly better than placebo for achieving Week 14 clinical remission and endoscopic improvement.[54] This trial enabled the European approval of vedolizumab for chronic pouchitis, a disease state with substantial unmet medical needs and few effective therapeutic options. Similar trials are being conducted in patients with other difficult-to-treat phenotypes, such as perianal CD and isolated ulcerative proctitis. For example, the recent ELEVATE trials of etrasimod enrolled a subset of ~10% of patients with isolated proctitis and demonstrated similar efficacy in this population that has historically been considered challenging to manage.[55]

Innovations in Measuring Late Phase Trial Outcomes

The current regulatory guidance for end points in registrational phase 3 trials includes a coprimary end point of clinical remission (CDAI <150) and endoscopic remission (Simple Endoscopic Score for CD ≤2 or Simple Endoscopic Score for CD ≤4 with no subscore >1) in CD and a composite outcome of clinical remission (total modified 9-point Mayo score of 0–1, stool frequency subscore 0 or 1, rectal bleeding subscore of 0, and centrally read Mayo Clinic endoscopy subscore of 0 or 1).[56,57] Although these instruments have some limitations that are detailed elsewhere,[48] the configuration of primary end points in phase 3 trials are generally aligned with current clinical treatment goals, particularly with the aim of achieving endoscopic remission in both CD and UC as a surrogate for potentially improving long-term outcomes, such as surgery, hospitalization, and future disease flares.[58,59] A previous international consensus has identified core outcomes that should be consistently measured and reported in IBD trials.[60] However, this space continues to rapidly evolve. Recent UC programs have measured more novel end points, such as urgency. In addition, multiple large-scale studies have now been launched that incorporate the use of intestinal ultrasound as a noninvasive repeatable measure of transmural healing in CD and there is increasing emphasis on evaluating histologic and/or combined histoendoscopic mucosal improvement in UC.[61,62] In the future, even more sensitive measures, such as assessment of intestinal barrier healing, may give greater resolution into the therapeutic efficacy of novel agents, although these are more likely to remain secondary or exploratory outcomes.[63]

Regulatory authorities have also emphasized the need to measure PROs to define treatment benefits and risks, although an IBD-specific PRO has yet to be fully validated. In the interim, 2-item PROs (stool frequency and rectal bleeding in UC, stool frequency and abdominal pain in CD) have been used, both demonstrating responsiveness to effective medical treatment despite capturing only a limited evaluation of the patient's disease experience.[64,65] D'Haens et al[17] have recently developed an 11-point Urgency Numeric Rating Scale, which captures clinically meaningful reductions in urgency-related symptoms. The Symptoms and Impacts Questionnaire for CD and UC is currently undergoing further validation and qualification for use in future registrational studies.[66]

Head-to-Head Comparison Trials

As therapeutic options for IBD have increased, understanding their relative efficacy and safety has become a key clinical question. Multiple head-to-head trials have now been completed in both UC and CD, assessing tumor necrosis factor antagonists, vedolizumab, IL12/23p40 and IL23p19 antagonists. Several lessons have been learned from these early experiences. First, the use of objective blinded end points is important because clinical measures may be biased by the absence of placebo. For

example, more than 60% of participants treated in the SEAVUE trial comparing adalimumab and ustekinumab in biologic-naive CD achieved clinical remission (higher rates than anticipated in the power calculations) and nearly 9 in 10 participants completed the 52-week trial, with all participants being aware that they were receiving active therapy.[67] Second, careful attention should be paid to blinding and follow-up procedures and ensuring that these are comparable between groups.[68] For example, SEQUENCE was an open-label study and while the trial demonstrated superiority for centrally evaluated endoscopic remission at Week 52 (32% vs 16%; $P < .001$), there was a significant difference in drop-out rates with 27.2% of ustekinumab-treated patients discontinuing early compared with 9.8% of participants receiving risankizumab. This contrasts with the findings from VIVID-1, where participants with CD were randomized 6:3:2 to mirikizumab, ustekinumab, or placebo in a rigorous treat-through, double-blinded, double-dummy design.[69] At Week 52, there was no significant difference between mirikizumab and ustekinumab for achievement of endoscopic remission (28.5% vs 27.9%; $P = .85$). Although these operational and logistical considerations for head-to-head RCTs in IBD can be complex, it warrants mention that direct, randomized comparisons remain the most robust evidentiary standard for comparative efficacy and safety of novel treatments.

Trials for Evaluating Treatment Strategies

Beyond placebo and active comparator parallel group trials for novel therapies, multiple late phase treatment strategy trials have changed IBD practice in the past decade. For example, REACT was the first cluster RCT in IBD, which evaluated an early combined immunosuppression (adalimumab and antimetabolite) regimen to conventional care: unlike individual patient randomized trials, REACT randomized gastroenterology practices to each study group and demonstrated that early combined immunosuppression reduced rates of major adverse outcomes including surgery, hospitalization, and serious disease-related complications.[70] Cluster randomization is advantageous for feasibly evaluating the impact of treatment strategies but is complex to design, less statistically efficient, and clustering effects must be considered in analysis. Similar cluster randomization methods were used in the REACT2 trial that evaluated whether treating to an endoscopic target was superior to conventional care.[71] Importantly, this trial demonstrated that while the primary outcome was negative on a population-level, the subgroup of patients with CD who have active inflammation (defined by C-reactive protein >5 mg/L) benefited the most from enhanced treatment. Other therapeutic strategy trials have used direct patient randomization. For instance, CALM was an open-label phase 3 randomized study demonstrating that patients treated to tight control (with timely sequential escalation based on fecal calprotectin, C-reactive protein, CDAI, and prednisone use) achieved superior clinical and endoscopic outcomes compared with standard care.[72] VERDICT is an ongoing phase 4 randomized study evaluating the optimal therapeutic target in UC, comparing patients who are treated to steroid-free symptomatic remission, endoscopic improvement, and histologic remission.[73] Although these studies integrate specific advanced treatments (adalimumab and vedolizumab, respectively), the primary results pertain to the therapeutic strategy that is evaluated (tight control or treat-to-target), rather than the efficacy of the agent itself given the other associated interventions in the trial. These types of trials are important for informing clinical practice recommendations, and they often consider a broader scope of patients than those enrolled only in registrational phase 3 studies. Accordingly, strategy trials often require a more pragmatic, rather than explanatory approach, for assessing treatment effectiveness and to ensure generalizability for routine care.[74]

Future Directions: What Will it Take to Modify Disease Outcomes?

Despite advances in IBD trial methodology, a transformative breakthrough in durable long-term remission has yet to be consistently achieved and true "disease-modification" may still be out of reach. Several potential solutions have been proposed. First, there has been interest in identifying a diagnostic, companion, or prognostic biomarker that identifies an enriched population who are potentially the most likely to respond to a particular therapy. Two examples should be considered. First, the addition of a "personalized" companion diagnostic assay (CDx) for TL1A was evaluated in the phase 2 ARTEMIS-UC study, evaluating tulisokibart (MK-7240, previously PRA023) in patients with moderately-to-severely active UC, demonstrating numerically higher rates of remission among those with CDx positivity.[75] The clinical application of this assay will be assessed in a phase 3 trial (NCT06052059). Second, the PROFILE trial was a multicenter, biomarker-stratified study, enrolling newly diagnosed CD patients (median time from diagnosis to enrolment was less than 2 weeks).[76] This trial used a 17-gene blood-based prognostic T-cell transcriptional signature (PredictSURE-IBD assay) that is associated with more aggressive CD phenotypes, and randomized patients to either a "top-down" or "step-up" treatment strategy. Disappointingly, there was no biomarker-treatment interaction effect to signal utility of measuring the assay before treatment. However, sustained surgery- and steroid-free remission among patients treated with top-down infliximab and immunomodulator therapy was 79% at 1 year, among the highest ever reported.

These studies highlight the failure of precision medicine approaches in IBD to date, which reflect the

complexities of the disease, multifactorial pathogenesis, heterogeneity in genetic and phenotypic presentation, and the still-limited understanding of the determinants of variability in treatment response. In the absence of a clear prognostic or companion biomarker, other authors have evaluated advanced combination therapy as a potential mechanism for breaking the therapeutic ceiling. Although several retrospective case series and open-label cohorts have suggested that combination biologic or small molecule therapy may be effective in patients with refractory IBD, this strategy had rarely been evaluated in a controlled setting.[77] Recently, the VEGA phase 2 POC trial randomized biologic-naive patients with moderate-to-severe UC to combination guselkumab and golimumab or to either agent as monotherapy for 12 weeks, followed by guselkumab or golimumab monotherapy.[78] At Week 12, a numerically higher proportion of participants receiving combination therapy had achieved clinical response (83%). Combination regimens have become increasingly attractive because of several factors: several agents approved for IBD have highly favorable safety profiles with limited systemic toxicity, and the advent of oral small molecules without risk of immunogenicity offers the potential for episodic exposure. As such, multiple combination trials are now planned or are recruiting (eg, DUET-UC NCT05242484 [guselkumab and golimumab], DUET-CD NCT05242471 [guselkumab and golimumab], NCT06227910 [vedolizumab and upadacitinib], NCT06095128 [vedolizumab and tofacitinib]). However, more work is needed to identify optimal combinations, ideally using drugs with orthogonal mechanisms of action, that are more likely to be synergistic or additive when combined.

Conclusions

There has been a substantive evolution in how trials are configured, which patients are recruited, what interventions are tested, and how outcomes are measured in IBD RCTs. Collectively, these changes have improved the overall efficiency of trial conduct while maintaining rigorous evidentiary standards and ensuring a patient-centered focus for clinical research. Adopting innovative strategies for future IBD RCT designs will be critical to overcome increasing recruitment, cost, and logistical challenges, and ensuring that the next generation of studies remains sustainable, generalizable, and informative for clinical care.

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Update on the Epidemiology and Management of Microscopic Colitis

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Microscopic colitis is an inflammatory bowel disease that commonly presents with debilitating chronic watery diarrhea. Recent epidemiologic studies and randomized trials of therapeutics have improved the understanding of the disease. Medications, such as nonsteroidal anti-inflammatories, proton pump inhibitors, and antidepressants, have traditionally been considered as the main risk factors for microscopic colitis. However, recent studies have challenged this observation. Additionally, several epidemiologic studies have identified other risk factors for the disease including older age, female sex, smoking, alcohol use, immune-mediated diseases, and select gastrointestinal infections. The diagnosis of microscopic colitis requires histologic assessment of colon biopsies with findings including increased in intraepithelial lymphocytes with or without expansion of the subepithelial collagen band. The pathophysiology is poorly understood but is thought to be related to an aberrant immune response to the luminal microenvironment in genetically susceptible individuals. Antidiarrheal medications, such as loperamide or bismuth subsalicylate, may be sufficient in patients with mild symptoms. In patients with more severe symptoms, treatment with budesonide is recommended. Maintenance therapy is often necessary and several potential treatment strategies are available. Biologic and small molecule treatments seem to be effective in patients who have failed budesonide. There is an unmet need to further define the pathophysiology of microscopic colitis. Additionally, trials with novel therapies, particularly in patients with budesonide-refractory disease, are needed.

Keywords: Lymphocytic Colitis; Collagenous Colitis; Diarrhea; Budesonide.

Microscopic colitis (MC) is an inflammatory bowel disease (IBD) characterized by chronic watery diarrhea.[1] The colon mucosa often appears normal while microscopically there is an increase in intraepithelial lymphocytes either alone (lymphocytic colitis) or in association with a thickened subepithelial collagen band (collagenous colitis). Incomplete MC describes patients with chronic diarrhea and either intraepithelial lymphocytes or a thickened subepithelial collagen band that does not meet thresholds for a classic diagnosis. In addition to diarrhea, patients commonly experience nocturnal bowel movements, urgency and fecal incontinence, abdominal pain, and weight loss, which cause impairments in quality of life and social isolation.[2] Effective treatments are available and improve quality of life and daily function. This article provides a comprehensive and evidence-based summary of MC epidemiology, pathophysiology, and treatments.

Incidence, Prevalence, and Temporal Trends

Recent studies found that the incidence of MC in Europe and select US populations ranges between 10.5 and 25.8 cases per 100,000 person-years.[1,3,4] Similarly, the prevalence of MC ranges from 197.9 to 246.2 per 100,000 persons.[1,3] In Sweden, the lifetime risk of MC was estimated to be 0.9% in women and 0.4% in men.[4] In the United States, data from Olmsted Country showed that the incidence of MC increased from 1985 to 2001 and stabilized between 2002 and 2019.[1,5,6] These results have been corroborated by 2 European studies.[3,4]

Risk Factors

Age

The risk of MC increases with age, with population-based studies reporting a mean age at diagnosis 60–64 years.[1,3,4] Nevertheless, cases of MC have been reported in all age groups including children.[7]

Sex

MC affects both sexes, but women are nearly 3 times more likely to develop MC than men.[4]

Abbreviations used in this paper: **IBD, inflammatory bowel disease; MC, microscopic colitis.**

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Race

Although MC should be considered in patients of all races and ethnicities, limited research suggests it is less common in Black, Asian, and Hispanic patients.[8] MC has been described in populations around the world and is likely more prevalent in diverse populations than suggested by current research.[9]

Alcohol and Smoking

Alcohol consumption and smoking are associated with an increased risk of MC.[10–12] A large prospective cohort study of women found a dose-dependent association with alcohol consumption,[10] whereas several observational studies have shown an association between smoking and risk of MC.[13] Compared with nonsmokers, current smokers have 3 times the odds of MC.[13]

Diet

Few studies have assessed whether diet is associated with risk of MC. There was no association between dietary intake of protein, carbohydrates, fats, or fiber or a lower-quality diet and MC in a population-based study.[12] Similarly, dietary gluten intake derived from food frequency questionnaires was not associated with MC in a cohort of US women.[14]

Obesity

Obesity and adult weight gain are associated with a reduced risk of MC in women.[15,16] The exact mechanism is not well-understood but may be related to hormonal effects of adipose tissue.

Medications

Many medications have been associated with MC. Aspirin and nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and selective serotonin reuptake inhibitors have all been associated with increased risk of MC.[17,18] However, the evidence was judged to be lower certainly because of presence of significant heterogeneity across previous studies and lack of associations when using colonoscopy or chronic diarrhea controls. Two recent studies that used patients with chronic diarrhea as a comparator group challenged these previous findings. Both studies found that most previously implicated medications (with the exception of nonsteroidal anti-inflammatory drugs in 1 study) were not associated with MC risk.[2,19]

Immune checkpoint inhibitors can induce a type of MC that may be more severe than sporadic MC and may require different treatment.[20] Management of checkpoint inhibitor–induced enterocolitis, including MC, was recently reviewed in this journal.[21,22]

Autoimmune Diseases

Autoimmune diseases are a risk factor for developing MC.[23,24] The most important is celiac disease. In a cohort study, individuals with celiac disease were more likely to have MC compared with control subjects.[25] The risk was highest during the first year after a celiac disease diagnosis, but remained elevated after 10 years of follow-up.[25] An estimated 6.7% of patients with celiac disease will be diagnosed with MC.[26] Ankylosing spondylitis, type 1 diabetes, Graves disease, Hashimoto thyroiditis, rheumatoid arthritis, multiple sclerosis, Crohn's disease, and ulcerative colitis have also been associated with MC.[24]

Predominant Antibody Deficiency Disorders Including Common Variable Immunodeficiency

A case-control study found an increased risk of MC in patients with predominant antibody deficiency, particularly in patients with common variable immunodeficiency.[27] Antibody deficiency should be considered in younger patients with MC and refractory symptoms.

Gastrointestinal Infections

Two large cohort studies showed an association between gastrointestinal infections and risk of developing MC.[28,29] In 1 study, infection with *Clostridium difficile*, *Norovirus*, and *Escherichia* species had the greatest risk,[29] whereas the other study showed an association with *Campylobacter concisus* infection.[28] In both studies, the risk was highest during the first year after infection but remained increased for years.

Family History

One previous cross-sectional study showed a higher risk of MC among those with family history of the disease.[30] Several common genetic variants have also been identified in genetic association studies for collagenous colitis.[31,32] Nevertheless, the collective contribution of genetics to development of MC has not been well-defined.

Presentation and Clinical Course

MC presents with multiple loose or watery bowel movements daily. In patients who have a colonoscopy for chronic diarrhea, 15%–30% will be diagnosed with MC.[2] Patients present with fecal urgency (93%), fecal incontinence (68%), weight loss (65%), nocturnal bowel movements (62%), and abdominal pain (52%).[2] Fatigue is often reported and may be caused by sleep disturbance from nocturnal bowel movements. Symptoms are worse in those patients with MC and a history of cholecystectomy.[2] MC can be misdiagnosed as irritable bowel

syndrome. The prevalence of MC is 4.1% among patients with irritable bowel syndrome with diarrhea.[33]

The natural history of MC is poorly defined. Some research suggests that long-term outcomes are promising, whereas other studies report significant risk for chronic symptoms.[34,35] In a recent prospective cohort study, 40% of patients with MC had a relapsing or chronic disease course 5 years after diagnosis. These patients had worse quality of life compared with those with a quiescent course.

A population-based cohort study found that individuals with MC are at slightly increased risk of death because of a greater burden of comorbidities.[36] Similarly, a second study found that individuals with MC were at increased risk of death because of smoking-related diseases,[37] although a US study showed no increase in mortality.[5] The increased risk of death in the first 2 studies is likely caused by residual confounding from smoking in patients with MC.

Diagnosis

A diagnosis of MC should be considered in any patient with chronic watery diarrhea (Table 1). Currently, there are no reliable blood or fecal biomarkers, including fecal calprotectin, to screen for MC. The diagnosis requires histopathologic analysis of $\geq$ 2 biopsies from the right colon and $\geq$ 2 biopsies from the left colon, rectum excluded.[38,39] Colonoscopy to the terminal ileum should be performed to rule out alternative diagnoses. The colon mucosa most commonly appears normal; however, macroscopic colonic findings can be seen in 17% of patients including erythema, erosions, scarring, and less commonly pseudo membranes, ulceration, or mucosal tears.[40]

The 2 major subtypes of MC are collagenous colitis (characterized by a thickened subepithelial collagen band [$>10\,\mu$m]) and lymphocytic colitis (characterized by >20 intraepithelial lymphocytes per 100 surface epithelial cells) with a lymphoplasmatic lamina propria infiltration (Figure 1). The subtype can change over time. In a large study, 1.6% of patients changed their MC phenotype from lymphocytic to collagenous colitis, and 0.5% from collagenous to lymphocytic colitis.[41] Incomplete MC describes patients with chronic diarrhea and either intraepithelial lymphocytes (5–20 per 100 epithelial cells) or a thickened subepithelial collagen band (5–10 μm) that does not meet the thresholds for a classic diagnosis.[42] The intraepithelial and lamina

Table 1. Key Considerations for Diagnosing and Managing Microscopic Colitis

Microscopic colitis should be considered in the differential for all adults with chronic, watery diarrhea.
Several autoimmune diseases and select gastrointestinal infections are risk factors for developing microscopic colitis.
Immune checkpoint inhibitors can induce a type of microscopic colitis that may be more severe and may require different treatment.
Microscopic colitis can be misdiagnosed as irritable bowel syndrome.
Microscopic colitis cannot be ruled out with blood or fecal biomarkers, including fecal calprotectin.
The diagnosis requires histopathologic analysis of $\geq$ 2 biopsies from the right colon and $\geq$ 2 biopsies from the left colon, rectum excluded.
Smoking cessation should be encouraged.
Stop a medication only if a clear temporal relationship with medication exposure and diarrhea onset. Long-standing medications with no association should not be discontinued.
In patients who report experiencing subjectively mild symptoms, antidiarrheal medications, such as loperamide, bismuth subsalicylate, or bile acid sequestrants, may be sufficient.
Mesalamine and systemic corticosteroids are not recommended as a treatment in microscopic colitis.
The primary treatment for inducing clinical remission in microscopic colitis is budesonide.
Maintenance therapy is often necessary for microscopic colitis.
After induction, most patients can be maintained on lower doses of budesonide, often as low as 3 mg per day or every other day.
To decrease budesonide dependence, loperamide or bile acid sequestrants can be used as adjuvant therapy.
Maintenance therapy with bismuth subsalicylate is not recommended.
Treatment should improve patient's symptoms and quality of life. Some have suggested that clinical remission be defined as a mean of <3 stools per day and <1 watery stool per day.
Budesonide failure is uncommon and requires further investigation. In cases with a remote diagnosis, repeat colonoscopy should be performed to confirm the diagnosis. Alternative diagnoses (celiac disease, ulcerative colitis, and Crohn's disease) should be ruled out. Antibody deficiency should be considered in younger patients.
Therapies reserved for ulcerative colitis and Crohn's disease (biologics and small molecules) are a treatment option for patients who fail budesonide. Consultation with an inflammatory bowel disease center is advised for patients who fail budesonide.

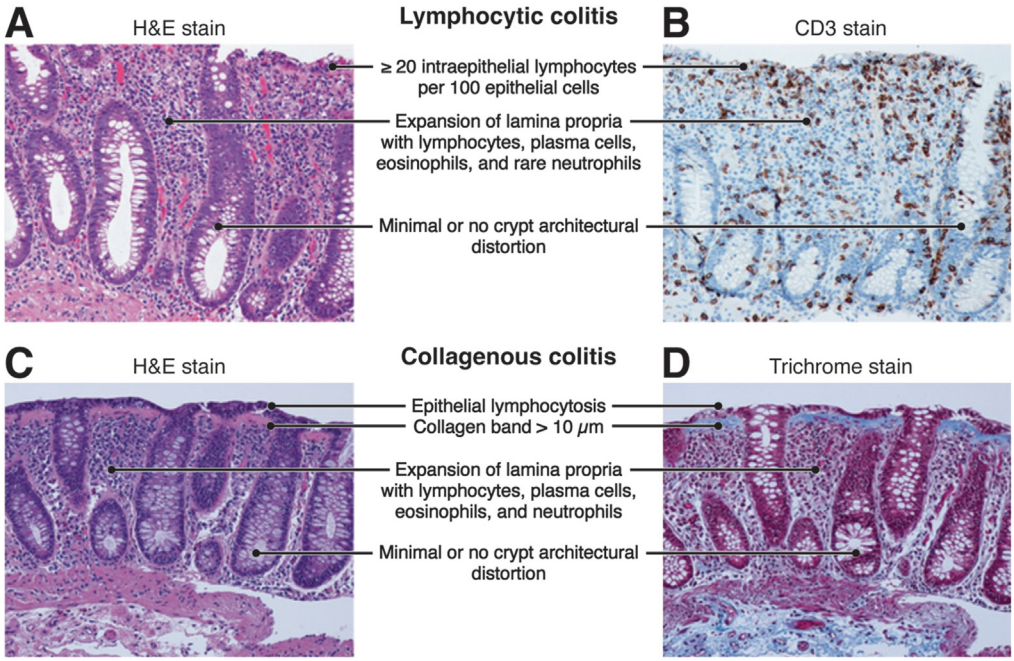

Figure 1. The 2 major subtypes of microscopic colitis are collagenous colitis and lymphocytic colitis. (*A*, *B*) Lymphocytic colitis is characterized by >20 intraepithelial lymphocytes per 100 surface epithelial cells. (*C*, *D*) Collagenous colitis is characterized by a thickened subepithelial collagen band (>10 μm) in combination with a lymphoplasmatic infiltration of the lamina propria. Image courtesy of T.C. Smyrk, Mayo Clinic.

propria lymphocyte density or thickness of the collagenous band are not associated with symptom burden.[43,44] MC histopathology is well described in other reviews.[45]

Outpatient follow-up to assess treatment response is critical after diagnosis. In a study of patients with a new diagnosis of MC, some patients were unaware of the new diagnosis, some were not treated for MC, and many remained symptomatic at 1-year follow-up.[46]

Pathophysiology

The pathophysiology of MC is largely unknown. Emerging evidence suggests that the disease occurs as a result of an aberrant immune response to the luminal microenvironment in genetically susceptible individuals (Figure 2). Here, we briefly highlight studies that have shed insight on disease pathophysiology.

Characterization of Immune Cells in Microscopic Colitis

MC is characterized by expansion of $CD8^+$ infiltration in the colonic epithelium and an increase in cytotoxic T cells (Th1, $CD8^+$) and T helper cells (Th17) in the lamina propria of patients with collagenous and lymphocytic colitis.[47–49] The intraepithelial lymphocytes in active collagenous and lymphocytic colitis demonstrate an increase in $Ki67^+$ staining[50] and a decrease in T-cell receptor excision circles,[51] which support possible local expansion of intraepithelial lymphocytes rather than thymic emigration of T cells.[47,50] Both subtypes of MC are also characterized by upregulation of chemokines secreted by epithelial cells that result in lymphocyte recruitment including CXCL9, CXCL0, CXCL11, and CX_3CL1.[52,53]

Genetic Association Studies

Previous studies have demonstrated a strong association between HLA Ancestral Haplotype 8.1 and risk of collagenous colitis,[31,32,54,55] but not lymphocytic colitis.[32,56] An enrichment of expression quantitative trait loci has also been detected with susceptibility variants for collagenous colitis in various cell types including intestinal cells.[31] Additionally, prior studies have shown polygenic pleiotropy between collagenous colitis and other immune-mediated conditions including Crohn's disease and ulcerative colitis.[31] The lack of the association between variants within HLA genes and risk of lymphocytic colitis may suggest differences in genetic basis of MC subtypes. Alternatively, most prior genetic association studies of lymphocytic colitis have had significantly lower number of cases and therefore may have been underpowered to find more modest associations with these variants.

Human Microbiome Studies

The microbiome has long been hypothesized to play a significant role in the pathogenesis of MC. In support of this, diversion of the fecal stream in individuals with refractory MC has been shown to result in histologic remission, followed by disease recurrence with reconnection of the fecal stream.[57,58] However, studies characterizing microbiome changes in MC have been small, mostly cross-sectional, and yielded no consistent findings.[59–63] Large-scale and longitudinal studies are

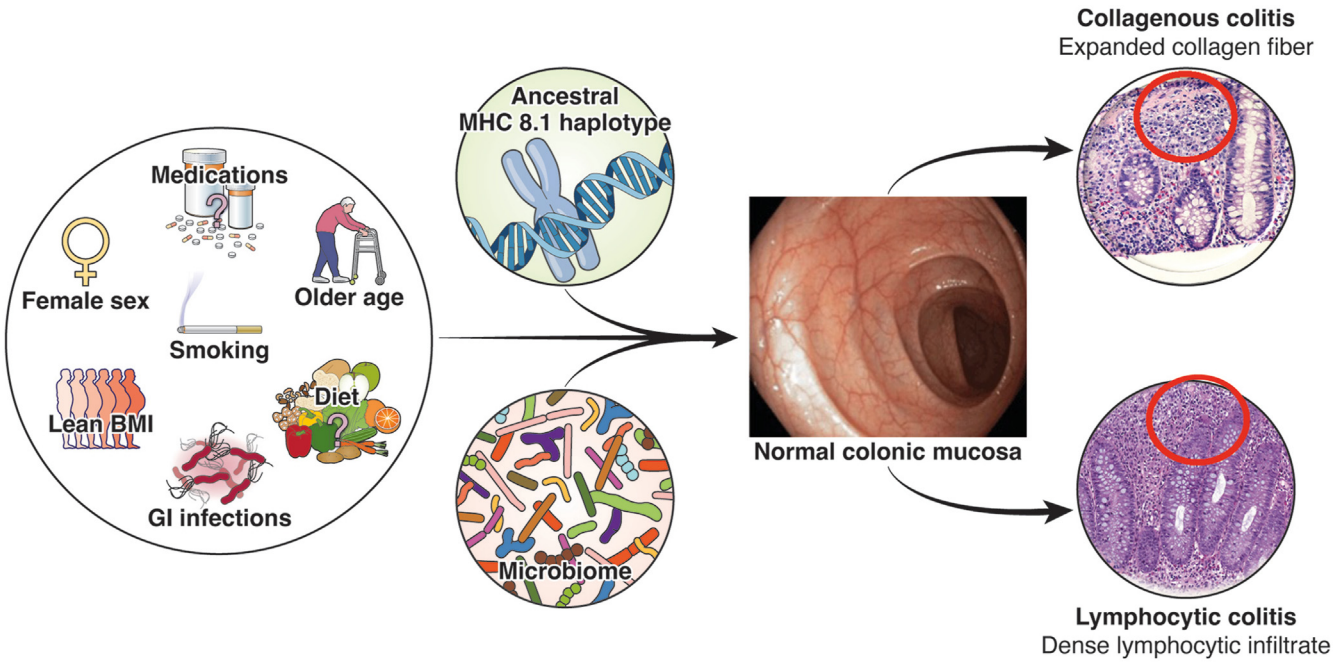

Figure 2. Microscopic colitis pathophysiology is poorly understood but thought to be related to an aberrant immune response to the luminal microenvironment in genetically susceptible individuals. Recent observational studies have challenged a potential role for diet and medication in the pathophysiology of the disease. BMI, body mass index; GI, gastrointestinal.

required to better characterize the role of the microbiome in the pathogenesis of MC.

Studies of Bile Salt in Microscopic Colitis

Bile acids have been proposed to play a role in the pathogenesis of both subtypes of MC. Small studies have shown abnormal 75 Se-homocholic acid taurine (^{75}ScHCAT) scintigraphy, a marker of bile acid malabsorption, in up to 60% of patients with MC.[64,65] Furthermore, there seems to be a significant decrease in expression of the main bile acid receptor, the farsenoid X receptor, in the right and left colon of patients with MC when compared with control subjects.[66] Given the known role of this receptor in suppressing inflammation and enhancing barrier function,[67] reduced levels of the farsenoid X receptor may contribute to the pathogenesis of MC through promotion of inflammation and increased epithelial permeability.

Studies of Collagen Deposition in Collagenous Colitis

The subepithelial collagen band in collagenous colitis is characterized mainly by type III and VI collagen, with small amounts of type I collagen.[68,69] These collagen types are normal products of subepithelial and pericrypt myofibroblasts and there is evidence that increased collagen production and impaired fibrolysis occur in collagenous colitis.[68,70–72] Increased collagen deposition is likely related to increased expression of transforming growth factor-β,[73] whereas higher expression of TIMP metallopeptidase inhibitor-1 in myofibroblasts derived from colonic biopsies of patients with collagenous colitis may in large part be responsible for impairment of extracellular matrix breakdown.[72]

Standard Therapies

There is no evidence to suggest that the management of collagenous and lymphocytic colitis should be different, so the treatment approach outlined here applies to both subtypes.

In some patients, there is a temporal association between starting a medication and the onset of diarrhea. Therefore, the first step in management includes assessing for such an association and stopping culprit medications (mainly proton pump inhibitors, nonsteroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitors) if an association is identified. Longstanding medications with no temporal association should not be discontinued. In addition, there is an association between smoking and MC, so smokers should be encouraged to stop.

An approach to medical therapy in MC is depicted in Figure 3. Response to treatment should be patient-centered and symptom-based. Treatment should improve patient's symptoms and quality of life. Some have suggested that clinical remission be defined as a mean of <3 stools per day and <1 watery stool per day (Hjortswang criteria).[74] It is not necessary to confirm histologic response to treatment.

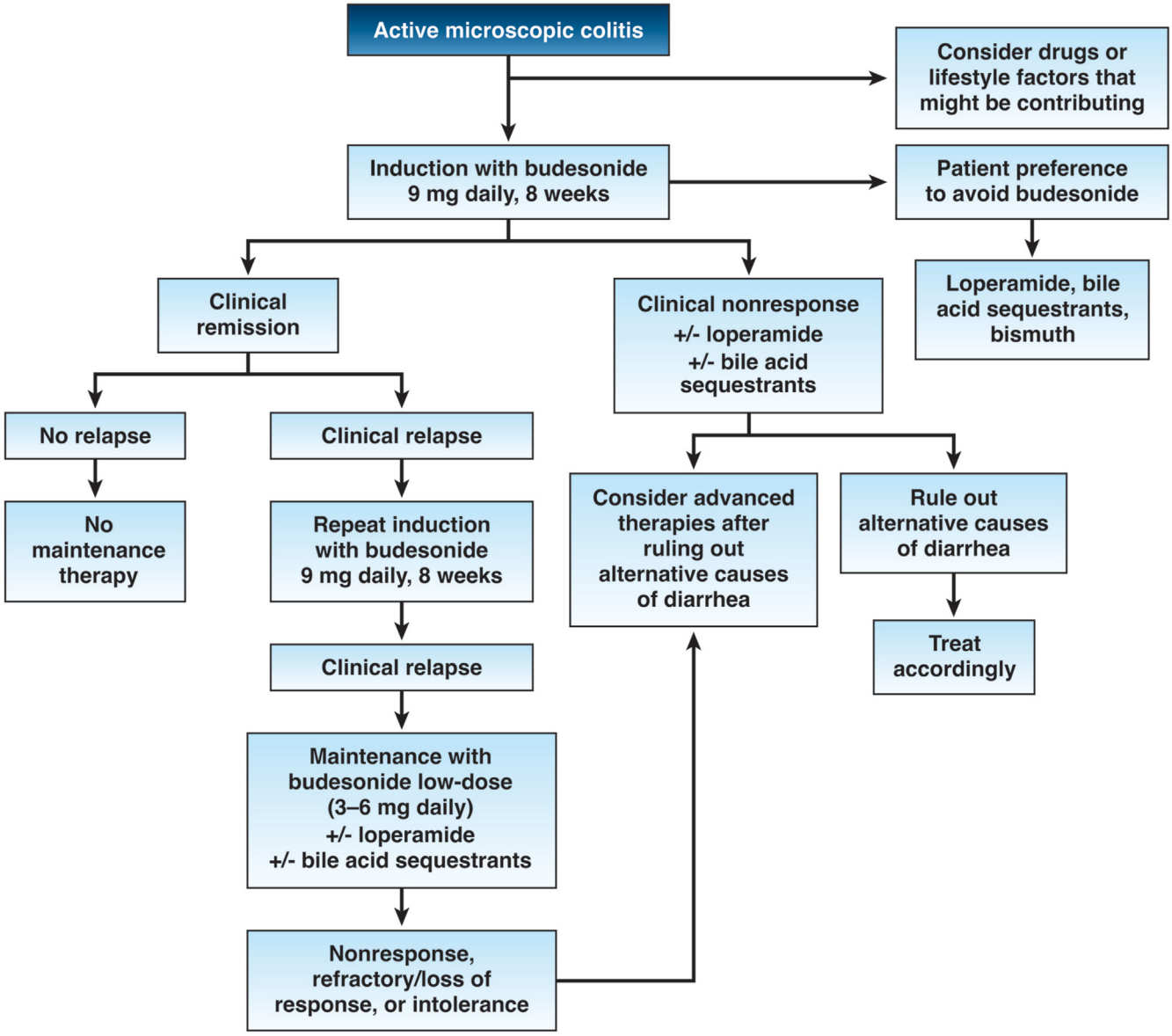

Figure 3. An algorithmic approach to treatment of microscopic colitis. Treatment should improve patient's symptoms and quality of life. Some have suggested that clinical remission be defined as a mean of <3 stools per day and <1 watery stool per day.

In patients with active symptoms of MC, budesonide (induction dose, 9 mg daily for 8 weeks) is recommended.[75] Budesonide is a corticosteroid with low systemic bioavailability because of high first-pass hepatic metabolism resulting in less side effects than other steroids.[76] Budesonide was superior to placebo in multiple controlled trials and in population-based cohorts.[77] A meta-analysis of 9 studies reported an odds ratio for induction of 7.3 (95% confidence interval, 4.1–13.2) compared with placebo with no increase in adverse events.[78]

The benefit of tapering budesonide is not clear. Some experts choose to taper over a few weeks to months after a standard induction course, whereas others do not. Select patients with severe symptoms may elect to not discontinue budesonide and instead taper to the lowest dose that maintains clinical remission.

Despite high rates of response to budesonide induction, recurrence after discontinuation is common (50%–80%).[77–81] A recent meta-analysis of 5 studies reported a pooled remission rate on budesonide maintenance therapy of 84%.[80] Because of data like this, the American Gastroenterological Association recommends budesonide for maintenance of clinical remission in patients with recurrence of symptoms following discontinuation of induction therapy,[82] although a population-based study showed that many patients could be managed with other drugs for maintenance, such as loperamide.[83]

The previously mentioned meta-analysis reported an odds ratio of 8.35 for budesonide compared with placebo for maintenance of remission.[78] Although budesonide is generally known to have less side effects during a short induction course, some providers have concerns about toxicity during maintenance therapy. However, most

patients can be maintained on lower doses for maintenance, often as low as 3 mg per day or every other day,[83] and several studies have reported no increase in steroid-related side effects during maintenance therapy.[78,83] Notably, some patients may not respond, become refractory, or intolerant to budesonide (Table 2).

In addition to budesonide, in some cases based on symptom severity and patient preferences, antidiarrheal medications, such as loperamide or bismuth subsalicylate (3 of 262-mg tablets 3 times a day for 6–8 weeks), may be sufficient, either alone or in combination with budesonide if the response is incomplete.[75] One previous meta-analysis reported response rates of up to 62% for loperamide and 75%, with 50% achieving remission, for bismuth.[84] However, prospective controlled trials are needed to better define the safety and efficacy of bismuth subsalicylate in MC. Maintenance therapy with bismuth subsalicylate is not recommended because of potential toxicity.[85,86]

Bile acid sequestrants are also another class of medication that is being used more frequently in the management of MC. Although no robust randomized controlled trials have been performed to evaluate these medications in MC, there is considerable open-label evidence to suggest these medications are effective, either as monotherapy[87,88] or in combination with budesonide to decrease budesonide dependence.[89] A meta-analysis of 9 studies reported a response rate of 60% and remission of 29%.[84]

Although mesalamine is sometimes used in MC, it was inferior to budesonide and no better than placebo in clinical trials in both lymphocytic[89] and collagenous colitis[90] and it is not recommended as a treatment in MC. Finally, the use of systemic corticosteroids in treating MC is poorly studied. Small studies suggest limited to no benefit.[77,91] Given the harms associated with systemic corticosteroid use and the availability of alternative therapies, systemic corticosteroid are no longer recommended to treat MC.[9]

Advanced Therapies (Immunomodulators, Biologic, and Small Molecules)

The primary treatment for inducing and maintaining clinical remission in MC is budesonide.[9] However, some patients experience budesonide failure and require advanced therapies, such as biologic therapy, and small molecules. Reasons to consider advanced therapy in MC are given in Table 2. Patients who fail budesonide often suffer from poor quality of life because of severe symptoms, inability to work, and subsequent disturbances in mental health.

Table 2. Indications for Advanced Therapy in Patients with Microscopic Colitis

Nonresponse	Clinical activity persists despite budesonide 9 mg induction therapy
Refractory/loss of response	Clinical activity despite budesonide 3–6 mg maintenance treatment
Intolerance	Unacceptable side effects from budesonide

Before initiating advanced therapies, an individualized therapeutic decision should be made. Repeat colonoscopy with biopsy is recommended if the diagnosis was established years ago, to confirm the diagnosis and rule out other causes of diarrhea. Furthermore, because celiac disease is associated with MC, especially in the refractory cases, it is important to exclude celiac disease.[92] An estimated 7.7% of patients with MC will be diagnosed with celiac disease.[26] A history of MC is also associated with an increased risk of Crohn's disease and ulcerative colitis, therefore clinicians should consider these diagnoses in refractory cases.[93] Another medication review should be performed to assess whether any new medications may be contributing to ongoing diarrhea.[9] Finally, smoking cessation is advisable, considering its association with reduced treatment response.[94]

Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) have shown limited efficacy in small case series.[95] Two systematic reviews on biologic therapy in MC have been published.[96,97] Both showed significant heterogeneity between studies. In the most recent paper, the pooled analysis of 14 studies (n = 164 patients) showed a remission rate for induction therapy of 63.5%, 57.8%, and 39.3% for vedolizumab, infliximab, and adalimumab, respectively. For maintenance, remission rates were 65.9%, 45.3%, and 32.5%. The rates of therapy limiting biologic-related adverse events were 12.2%, 32.9%, and 23.0%, respectively.[97]

In a separate article, tumor necrosis factor inhibitors (infliximab and adalimumab) demonstrated a response rate of 73% with a remission rate of 44%. The response rate for vedolizumab was similar; 73% response with a remission rate of 56%.[96]

In a large retrospective European series, 99 patients with MC were treated with advanced therapies. Anti–tumor necrosis factor agents were commonly used as first-line options, however, with frequent discontinuation because of nonresponse or loss of efficacy over time. Vedolizumab and ustekinumab were often given as second- or third-line therapies, whereas JAK inhibitor–treated patients exhibited the highest remission rate, albeit with a small sample size (n = 14).[98]

Advanced therapies should be considered in patients who fail budesonide. Despite the lack of approval of these drugs for MC, the pathophysiological overlap with IBD suggests a similar treatment approach. Hence, referral to an IBD center with advanced therapy experience is recommended for severe cases. Although anti–tumor necrosis factor agents exhibit good remission rates and fast onset of action, vedolizumab's advantageous safety profile is crucial for older patients with

comorbidities and in 1 of the systematic reviews was better with respect to maintenance therapy and safety. JAK inhibitors show promise but necessitate further investigation, particularly regarding adverse events. In severe cases of MC, surgery may be required when all medications fail.

Health Care Maintenance

Small studies suggest patients with MC are at increased risk for osteoporosis or osteopenia compared with control subjects.[99] Budesonide use was associated with a dose-related risk of fractures.[100] However, another study showed no increased risk of osteoporosis or other steroid-related adverse events, even when budesonide was used for maintenance therapy.[83] MC patients on budesonide maintenance therapy may benefit from supplementation with calcium and vitamin D. Unlike IBD, MC is not associated with an increased risk of colorectal polyps or cancer.[101,102] Patients with MC treated with immunomodulators or biologic therapy may be at increased risk for infections. These patients may benefit from the vaccination recommendations for patients with IBD receiving immunosuppressive therapy.

Conclusions

MC is a common cause of chronic watery diarrhea in older adults that impacts quality of life and daily functioning. Although the understanding of MC has advanced, there is an unmet need to determine noninvasive biomarkers, to further define pathophysiology, and to position treatments in patients who fail budesonide.

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Conflicts of interest
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