Challenges in IBD Research 2024: Pragmatic Clinical Research

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Introduction to the Pragmatic Clinical Research 2024 Workgroup

Pragmatic clinical research is one of five focus areas of *Challenges in IBD Research 2024*, which also includes preclinical human inflammatory bowel disease (IBD) mechanisms, environmental triggers, novel technologies, and precision medicine.

Important progress has been made via pragmatic clinical research since *Challenges in IBD 2019*[1], including the first head-to-head biologic trials to aid in better understanding how to position drug therapies and many studies assessing the utility of therapeutic drug monitoring (TDM) and incorporating TDM into dashboards to assist in clinical care and achieving tighter disease control. Yet significant gaps remain and require ongoing work as outlined in this document.

In *Challenges in IBD Research 2024*, pragmatic clinical research is defined, as it was in 2019, as research that will directly and positively impact patient care by addressing important clinical questions. Pragmatic clinical research should also evaluate and promote the systematic uptake of evidence-based findings into routine practice. Pragmatic clinical research utilizes methodologies that study people either through direct interaction with individuals and/or indirect interaction by studying large databases, such as registries and administrative claims data. The expectation is that research findings that address these research areas will result in changes in how patients are treated through highly cited publications that will influence clinical guidelines and health policies.

When considering research gaps in the field and priorities for *Challenges in IBD Research 2024*, there are three main phases of focus during the disease course of IBD: interception, remission, restoration. However, since the study of the preclinical phase (prior to symptoms occurring) of IBD is still developing, and it remains unclear who, when, and how to screen for IBD, the Pragmatic Clinical Research Workgroup focused on biomarkers and therapeutic interventions for

patients with established clinical disease. The goal was to optimize available diagnostics and treatments to maximize the number of patients achieving and maintaining remission, as a steppingstone to restoration of normal functioning in the long term.

In particular, the Pragmatic Clinical Research Workgroup focused on clinical research that is needed to define optimal patient care and to implement approaches needed to achieve optimal care as standard practice in IBD to reach the best outcomes for patients. The Workgroup also focused on barriers to care and the need for timely and equitable access to care for all patients. The priority research gaps identified to address through pragmatic clinical research (**Figure to come)**, after considering the progress from the last five years, include:

1. Achieving optimal clinical outcomes in adults and in children with IBD, including historically understudied groups, to improve remission rates and restoration of quality of life;
2. Validating biomarkers for early diagnosis and as predictors of treatment response in adults and children with IBD to aid in improving treatment resulting in better outcomes in remission and restoration; and
3. Determining the optimal selection and timing of treatment (medical, surgical, adjunct) in adults and children with IBD.

Priority Gap #1: Achieve optimal clinical outcomes in adults and children with IBD to improve remission rates and restore quality of life

Priority Action #1: Address understudied patient groups to improve their likelihood of achieving remission and restoration.

Considering the rising prevalence of IBD across an increasingly diverse global population, it is imperative to broaden the scope of research to include historically underrepresented patient

groups.[2,3] Traditionally, industry-led clinical trials have been predominantly composed of relatively homogenous patient groups, primarily consisting of predominantly non-Hispanic White individuals receiving their IBD care at large academic centers.[4–6] In fact, 91% of participants in placebo-controlled induction trials and 92% of maintenance trials for the novel therapies approved by the United States Food and Drug Administration (FDA) for CD were non-Hispanic White.[7] Further alarming is that clinical trials frequently neglect to report basic demographics, and it is common to report findings of entire populations without disaggregating reporting by age groups.[8,9]

Diversity in IBD research is critically needed as demonstrated by several key studies that have observed differences in clinical remission and endoscopic healing in response to biologics by race and age.[10–13] Moreover, prior studies have identified that children with very early onset IBD (VEO-IBD) demonstrate more rapid biologic clearance[14–16] and are often more treatment refractory to the anti-TNF biologics compared to children with later-onset IBD.[17] Additional areas that have been historically understudied include management of perianal CD, ulcerative proctitis, and treating functional or mental health disabilities (fatigue and chronic pain) even when deep remission has been achieved.[13,18–22]

With a growing therapeutic armamentarium, it will be crucial to investigate drug efficacy and safety in historically underrepresented extremes of age, including the very early onset (<6 years old), early onset (<10 years old), and older onset (>65 years old) populations of patients with IBD. For comprehensive transparency, both observational and placebo-controlled clinical trials should diligently report patient demographics, encompassing socioeconomic status, educational background, geographic location, health literacy and access to healthcare. Additionally, it is critical to meticulously account for patient age, including disaggregating age groups for young children, adolescents, and young adults, as well as ethnicity and race when presenting findings related to pharmacometrics, drug efficacy and drug safety. With increasing availability of therapeutics using different mechanisms of action, it will also be important to evaluate efficacy

and safety based on genetic and immune phenotypes to enhance the applicability of clinical trial findings in real-world clinical practice.[4] These investigations may include a broader examination of the HLA-DQA1*05 variant on anti-TNF immunogenicity in non-White, and non-adult cohorts[23] or a more inclusive validation of cellular modules in subsets of IBD patients to better personalize biologic selection.[24,25]

In order to address these gaps, clinical trials, and initiatives such as CAPTURE IBD, SPARC IBD, and others[26] will need to employ innovative strategies to achieve diversity and inclusion of underrepresented patient populations.[27,28] Potential strategies include collaborating with community liaisons to address issues of medical mistrust, health literacy, and other potential roadblocks to enrollment; and to offer creative solutions such as monetary compensation that accounts for the costs of participating in research (missed work, travel, and others)[29]. Moreover, to ensure a more inclusive population representative of the IBD landscape, researchers will need to leverage virtual technology (such as scheduling telemedicine visits for reviewing consent forms or follow up visits), engaging multiple stakeholders and pharmaceutical companies to select trial centers based on a previously underrepresented geographical area.

Priority Action #2: Standardize interventions and monitoring of disease response and patient outcomes more effectively to achieve better outcomes for remission and restoration

Despite advancements in novel therapeutics, the progressive inflammatory burden of IBD poses a substantial lifetime risk of disease-related complications[13,30,31] and adversely affects overall well-being.[22,32] The Selecting Therapeutic Targets in IBD initiative (STRIDE-II) has evolved to provide updated treatment targets for both adults and children with IBD, emphasizing near- and long-term goals of clinical and biochemical remission, endoscopic healing, elimination of disability, achievement of normal growth in children and the restoration of QOL.[33] The STRIDE-II guidelines

underscore the significance of patient engagement in their health. Furthermore, these guidelines highlight the importance of frequent reassessments, not only focusing on objective measures such as biochemical, endoscopic and growth indicators, but also recognizing the priority of subjective measures such as symptom control, patient functioning, and overall health restoration for patients living with IBD.

In response to the call for standardized interventions, several pragmatic clinical trials have been conducted recently. Notably, a large double blinded, randomized placebo-controlled pragmatic clinical trial in children with CD of anti-TNF monotherapy vs. combination with oral methotrexate, demonstrated superiority of combination therapy among the subset of patients on adalimumab in clinical practice without standardized dosing or routine therapeutic drug monitoring (TDM).[34] In a randomized trial of adults with immune-mediated inflammatory diseases (IBD, arthritis or psoriasis), those assigned to the TDM arm had a significantly higher rate of sustained disease control without disease worsening compared to those assigned to the standard therapy arm.[35] In a head-to-head comparative effectiveness trial for moderate to severe UC that did not allow for dose escalation, vedolizumab was found to be superior to adalimumab in achieving rates of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission.[36] Moreover, trials assessing high dose adalimumab regimens revealed varying efficacy in UC and CD[37,38] which found notable differences in children with UC that subsequently resulted in a change in adalimumab dosing recommendations for children from the FDA.[39]

Since the real-world effectiveness of novel IBD therapies may not align with the efficacy reported in clinical trials, it is essential that funding agencies continue to support pragmatic clinical trials and studies of real-world data. Moreover, although the feasibility of assessing all STRIDE-II standards for each trial may be limited by resource constraints, there are several key gaps that prior studies did not address that require further investigation. These include assessing short (under 2-3 years) and long-term (multi-year) remission (clinical, biochemical, endoscopic, and

restoration of QOL) between combination therapy and biologic monotherapy guided by proactive TDM in subgroups of patients that have been historically understudied, such as children, older adults, and those with perianal CD, ulcerative proctitis, and isolated upper tract disease. Frequently, the reported effectiveness and safety of combination biologics or the combination of a biologic with a small molecule medication are confined to small case series. There is also a gap in the evidence evaluating the use of pharmacodynamic biomarkers such as abdominal ultrasound or fecal calprotectin to systematically guide therapy intensification to improve outcomes. Finally, trials will need to investigate whether treating to the targets of histological healing in UC or transmural healing in CD will lead to superior long-term outcomes without increase in treatment-related adverse events than endoscopic healing as a target.

There remains ongoing uncertainty surrounding the use of proactive TDM or non-invasive biomarkers for predicting treatment response, and in which patients they may be beneficial or ineffective.[40–43] It is therefore imperative for funding agencies to not only provide support for these essential investigations, but also require that investigative teams diversify their enrollment criteria to ensure findings are generalizable to all patient populations. These requirements will aid in identifying subsets of patients who may or may not benefit from these innovative strategies and provide evidence where personalized care may improve outcomes for patients with IBD. As regimen intensification has restored health for many receiving biologic and small molecule therapies, it will be imperative for future studies to investigate the pharmacokinetic and pharmacodynamic criteria to identify when and if step-down therapy can be effectively undertaken while maintaining health restoration. Careful consideration should also be given to implementation of at-home monitoring (via home testing assays, etc.) or use of on-body devices to streamline care and improve active engagement with the patient. Future investigations should also evaluate the use of digital tools (telemedicine, remote monitoring, smartphone applications, and web-based portals) to improve health related QOL and patient reported outcomes. Finally, as novel therapies

restore intestinal health and function, it will be key to systematically assess more subjective outcomes of patients suffering from IBD-related comorbidities such as depression, anxiety, or irritable bowel syndrome.

Priority Action #3: Address barriers to care to improve remission and restoration

Identifying and addressing barriers to care for people living with IBD is a critical aspect of improving remission rates and restoring QOL. Social determinants of health (SDOH) or the "conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life"[44] exert a greater influence on health and disease than direct medical care alone.[45–47] Previous work has highlighted a link between IBD outcomes and SDOH, such as financial toxicity[48–51], food insecurity[52,53], and social support[52]. In addition, while rapid advancement in therapies for IBD have revolutionized the ability to achieve remission, uptake of these advanced therapies is suboptimal.[54,55] Identified barriers to uptake and use of advanced therapies include delays in diagnosis[56,57], insurance coverage of evaluation and treatment[58–65], suboptimal patient-centered communication[66–69], and access to care itself.[66,67] Addressing barriers to care for people living with IBD must, therefore, be approached at multiple levels of the patient, health care professional, payer/insurance, and health system.

Recent progress in understanding barriers to care has implicated insurance delays, and denials of treatment authorization as leading to worse disease outcomes.[59,60,65,68,69] However substantial gaps in the evidence remain in how these barriers are affecting underrepresented populations, and there remains little evidence to support mitigating strategies. There also has been important progress in evaluating and improving shared decision making, including a cluster randomized trial of decision making related to treatment decisions, and refinements in decision aids.[70–74] However, gaps remain in the evidence of how best to implement shared decision making, and further studies on the impact of using decision aids as well as other approaches for educating and engaging

patients in discussion of treatment options, are needed, particularly in patients with varying levels of educational attainment and varying socio-cultural backgrounds.[70,75,76] There has also been some progress on evaluating multidisciplinary care including the importance of mental health care for patients with IBD.[77] However, evaluations of innovative modes of integrating multidisciplinary treatment in IBD care as well as approaches to improving costs of value-based care are still needed. [77–79]

To address these gaps, investments should be made in investigating the barriers to care at every level including early identification of patients with potential IBD prior to GI referral, understanding workforce issues and access to GI care, understanding the diagnostic delay for patients with varying presentations of disease or uncommon phenotypes. We recommend further research into medical decision-making for all patient populations, including the role of 3rd party payors in influencing the clinician-patient relationship and informed decision making. Research is also needed to understand the impact of treatment delay with attention to time-to treatment and prevention of disease-related complications. Shared decision-making research is also needed to further understand patient values regarding treatment decisions and both short-term and long-term outcomes.

Priority Gap #2: Use of and validation of biomarkers for early diagnosis and as predictors of treatment response in adults and children with IBD to result in better outcomes in remission and restoration

Priority Action #1: Validate use of existing biomarkers in different IBD patient subgroups

The use of biomarkers has the potential to benefit patients by improving individualization of treatment and monitoring response to therapy. Some biomarkers may serve as surrogates to

endoscopic evaluation, while others may provide prognostic information or help identify optimal treatment mechanisms or dosing. Progress has been made in each of these areas. However, current available biomarkers have been evaluated under limited conditions. For a biomarker to be broadly useful in practice, it should be accurate and reliable in all patient populations inclusive of age, gender, race, or ethnicity. It should also function equally well in all disease phenotypes and extents of disease, and across the range of disease activity. There is a pressing need to evaluate and validate biomarkers for use in the full range of populations to benefit all patients with IBD.

Since the *Challenges in IBD Research* 2019, substantial progress has been made in developing and validating biomarkers. Recent studies demonstrated the reliability of fecal calprotectin for postoperative monitoring.[80,81] Several studies have evaluated fecal calprotectin for identifying pouchitis in patients with ileal pouch anal anastomosis (IPAA).[82] The magnitude of the calprotectin increase was found to be associated with severity of endoscopic findings in patients with pouchitis [83], is sensitive to change in disease activity after treatment[84], and may be associated with disease outcomes.[85] Other studies have demonstrated its reliability for patients with ileostomies.[80] Still others have evaluated fecal calprotectin in other patient populations. Recent studies have demonstrated the time trends of fecal calprotectin during pregnancy[86], and demonstrated the ability of calprotectin to predict disease exacerbation.[87] However, in other settings, such as for patients with proximal small bowel disease, there remains little reliable evidence.[40]

For prognostic indicators HLA DQA1*05 was found to be associated with risk of developing anti-drug antibodies among patients on anti-TNF medications.[23] However, there has been little prospective data to date, and limited evaluation in non-White patients.[88] There also have been inconsistent findings, particularly in pediatric studies.[89,90] Several panels and dashboards have been developed for monitoring therapy.[91,92] Others evaluate combinations of serologic markers to serve as surrogates for endoscopic activity such as the endoscopic healing index (EHI), and the mucosal inflammation non-invasive index (MINI), each of which have undergone limited testing

and need to be evaluated prospectively in broader populations to demonstrate their reliability and reproducibility.[40,93–95]

Despite this important incremental progress, there remain patient populations for whom these biomarkers have yet to be evaluated. With the growing incidence of IBD, increasing incidence of VEO-IBD and increasing prevalence in the elderly, each of these biomarkers needs to be evaluated and validated across the entire age spectrum. The new panels need to be evaluated in diverse patient populations as well. It is also important to evaluate these biomarkers in disease phenotypes that have been understudied including in patients with isolated proximal bowel disease, limited proctitis, J-pouches, and perianal and internal penetrating disease.

To address these important gaps, it will be necessary to conduct prospective studies evaluating all existing and novel biomarkers in each of these patient populations. It is important to specifically study biomarkers in non-white populations, in children, and in the elderly. It is also important to evaluate them in patients with disease phenotypes that have been understudied. Investigators need to report results of studies for each of these populations and to disaggregate age groupings so not all children's results are grouped together. Younger children may have different findings than older adolescents. Similarly, biomarkers may have different efficacy in younger adults than in older adults. Therefore, study findings should be reported by age subgroups in addition to race, ethnicity, and disease phenotype.

Priority Gap #3: Determine the optimal selection and timing of treatment (medical, surgical, adjunct) in adults and children with IBD

Priority Action # 1 – Comparative effectiveness of therapies, diets, surgeries, etc. in IBD

As treatment options for managing IBD continue to expand, and treatment approaches become more complex, there is increasing need for comparative effectiveness research (CER) to inform optimal positioning of therapies and implementation of treatment strategies.

In the interim since *Challenges in IBD 2019*, pivotal comparative efficacy and pragmatic clinical trials as well as large observational CER studies have moved the field forward. Industry sponsored head-to-head trials like VARSITY (comparing vedolizumab vs. adalimumab in patients with moderate-severe UC) and SEAVUE (comparing ustekinumab vs. adalimumab in biologic-naïve patients with moderate-severe CD) have informed positioning of biologic agents.[96,97] Pragmatic clinical trials like DINE-CD (comparing specific carbohydrate diet vs. Mediterranean diet in patients with CD), COMBINE (comparing TNF antagonists with low dose methotrexate vs. TNF antagonist monotherapy in pediatric CD), and SPARE (comparing treatment de-escalation strategies patients with CD in stable remission) have adopted a patient-centered approach to addressing questions of great relevance to clinical practice.[34,98,99] Observational comparative effectiveness and safety studies have helped compare risk of serious infections with different advanced immunosuppressive therapies in real-world practice and helped address fundamental management questions such as early surgery vs. medical management for CD.[55,100–103]

Over the next 5 years, these comparative effectiveness questions will continue to be paramount. As treatment options evolve, and head-to-head trials lag, comparing the effectiveness and safety of different pharmacological agents as well as other disease management strategies will be immensely important to broadly inform treatment positioning and approach in real-world practice. Recognizing differences in individuals, large studies that address heterogeneity of treatment effect to facilitate personalization of therapy based on usual clinical parameters would be vital. These CER studies would extend beyond just pharmacological agents, to include the role of different dietary and microbiome-directed interventions (as adjunct to usual therapy), integrative

and behavioral health strategies, different surgical approaches, etc. Additionally, comparison of different disease monitoring strategies such as endoscopy- vs. biomarker-based monitoring in diverse settings such as luminal or post-operative CD, treatment monitoring strategies such proactive vs. reactive vs. genotype-guided TDM for TNF-antagonists and other advanced therapies, and real-world comparison and implementation of treat-to-target strategies including treatment escalation in asymptomatic patients with ongoing bowel inflammation would be vital. Just as timely escalation is critical to minimizing disease-related disability, studies comparing treatment de-escalation approaches in patients in deep remission will help inform approaches to decreasing treatment burden and improving patients' QOL. While these questions are widely applicable to most patients with IBD, special attention would be required in CER studies to focus on patients historically excluded from clinical trials – these include racial, ethnic, and gender minorities, older patients as well as patients with VEO-IBD, patients with J-pouches who experience antibiotic-dependent or refractory pouchitis, small bowel stricturing CD, perianal and internal fistulizing CD, patients with ostomies, patients with ulcerative proctitis, patients with predominantly extra-intestinal manifestations, etc. The outcomes on these comparative effectiveness studies need to extend beyond conventional measures of symptomatic and endoscopic remission, to address more patient-centered outcomes such as fatigue, multi-dimensional QoL, disability, surgery, and treatment burden.

Addressing these pivotal CER questions requires adopting a variety of different research approaches. Well-conducted comparative efficacy- and pragmatic effectiveness clinical trials, designed as superiority, non-inferiority or equivalence trials, provide the highest level of evidence to support one intervention over another.[104,105] However, RCTs are expensive, take a long time to complete, are generally too small to detect rare outcomes, too short to detect long-term effects, often too simple and underpowered to examine heterogeneity of treatment effects, and are selective in inclusion which limits generalizability. Alternative approaches to CER are therefore

warranted to complement and/or supplement these findings. Non-trial approaches can rely on indirect comparison of data from existing trials through trial-level network meta-analyses, or through pooled analyses of participant-level data from clinical trials.[106] Observational CER performed using real-world data will be pivotal in moving the field forward. Several different real-world data sources exist, including electronic health records, administrative claims databases, disease and product registries, and patient-generated health data from surveys, patient-reported outcomes, mobile applications, etc.[107] These non-interventional, observational data sets rely on data collected during routine clinical practice, from diverse patients, in the context of real-life decision-making. CER studies using these data can be used to ascertain comparative effectiveness and safety of different management approaches after accounting for key drivers of decision-making. They have advantages of being more inclusive and often have larger sample sizes which can address safety concerns not addressed in trials but have the disadvantage of having non-random treatment allocation. Advanced statistical methods such as propensity score methods and target trial emulations can potentially overcome some of these limitations. All in all, while many knowledge gaps exist within the field of CER in IBD, with the careful study approaches, these gaps can ultimately be addressed and more patients along the way will have a better chance of remission and improved quality-of-life despite living with IBD.

Priority Action # 2 – Surgical therapies

Surgical treatment selection

The management of CD and UC often involve critical decisions regarding the role and timing of surgery. In patients with CD, surgery is typically reserved for cases where the disease is refractory to medical therapy and for complications such as strictures or fistulas. The expanding landscape of medications has improved the ability to control inflammation of IBD, resulting in a trend toward

fewer surgeries.[108–110] As a result, those who do undergo surgery are often sicker patients with more refractory disease. This shift toward more complex disease presents new challenges. At the same time, recent studies such as the Laparoscopic Ileocecal Resection versus Infliximab for Terminal Ileitis in Crohn's Disease (LIR!C) and the Swedish Crohn's trials, raised important questions about the timing and positioning of surgery relative to medical therapy for CD.[111,112] However, identifying those patients who may benefit from early surgery has not yet been fully elucidated. Newer techniques such as Kono-S anastomosis and other mesentery excision techniques may improve outcomes and may reduce the risk of disease recurrence.[113] However it remains unclear what aspects of the surgery are responsible for improved outcomes. Further, evidence-based strategies are lacking for identifying patients at low-risk for disease recurrence, or for identifying which patients, if any, may not require postoperative medical therapy for CD.[114–117]For patients with perianal fistulas, the optimal surgical technique and timing also remain unclear.[118–120] Stratifying which patients require seton placement, duration of seton, and optimal technique for repair of rectovaginal fistula all require further research.[120–122] Of great interest to patients is ostomy surgery, and how to optimize conditions to enable closure.[55,123–125] Additional gaps in the literature include identifying the optimal timing for surgery, taking into consideration factors such as the disease location and phenotype, patient nutritional status, age, height, and growth potential (in children). Further, reliable, disease-specific, and anatomy-specific Patient-Reported Outcome Measures (PROMs) are needed for assessing patient outcomes following IBD surgery. Unfortunately, there is significant heterogeneity in the currently available PROM instruments.[126]

To address these gaps will require multidisciplinary and multicenter collaborations. It will be necessary to support the development of multidisciplinary collaborations to facilitate these important studies. It is also essential to address these gaps in underrepresented populations such as children, the elderly, pregnant patients, etc.

Priority Action #3 - Combination and adjunct therapies

There has been growing interest in the use of combinations of advanced therapies to fill the need for effective treatment for patients whose disease is non-responsive to any single advanced therapy. This has most commonly been documented as vedolizumab in combination with either anti-TNF medications or ustekinumab, although combinations with janus kinase (JAK) inhibitors have been reported as well.[127–131] Limited evidence suggests efficacy among adults and children with active disease despite multiple prior advanced therapies.[127,129] Infections have been described, and appear to be infrequent.[128,129,131] However, no prospective or large-scale studies have been conducted.

Increasing evidence suggests diet may play an important role in disease development and in the attenuation of symptoms and inflammation.[132] Since *Challenges in IBD Research 2019*, there have been numerous advances in the field of diet in IBD, both in our growing understanding of the intricate relationship between diet, the gut microbiome, functional metabolites. A recent study comparing the specific carbohydrate diet (SCD) to the Mediterranean diet in patients with Crohn's disease found that both diets equally improved clinical symptoms.[98] Around the same time, several prospective intervention and observational studies demonstrated the benefit of adhering to a Mediterranean diet on clinical and biochemical disease activity in patients with Crohn's and UC.[133–135] Furthermore, the low FODMAP diet, which may improve symptoms in patients with irritable bowel syndrome and quiescent IBD, did not demonstrate efficacy in the improvement of inflammation in IBD in a well-conducted randomized trial.[136] Although there are a greater number of studies evaluating the potential role of diet as therapy for Crohn's disease, there are a few studies evaluating diet in UC. One recent uncontrolled study demonstrated higher fiber, lower fat diet may improve the quality of life and reduced dysbiosis in patients with UC.[137] Taken altogether,

in the last 5 years, there has been an increase in the quality of evidence supporting a role for diet in treatment of IBD, but it remains unclear in whom and under what conditions can dietary therapy be used to treat IBD.

Beyond studies examining diet as potential therapy, other studies have examined the impact of nutritional status on disease outcomes. For instance, malnutrition and sarcopenia, commonly found among patients with IBD, can impact disease outcomes. They are associated with increased risk of hospitalizations and worse post-operative outcomes in patients with CD.[138–140] At the same time, while studies examining probiotic therapies in IBD remain underwhelming in their results, a growing number of clinical studies demonstrate the efficacy of high-dose curcumin in improving symptoms and endoscopic findings in UC.[141–143] These studies, therefore, highlight the importance of balanced nutritious diet such as with the Mediterranean diet to prevent malnutrition and improve symptoms. Further research is needed to identify specific ingredients which may be associated with improved inflammation in patients with IBD.

A few studies have identified that lifestyle factors such as psychological stress, lack of physical activity, and sleep may increase the risk of IBD flares.[144,145] Lack of sleep is common among patients with IBD, even when the disease is well-controlled.[145]. One study evaluated the combination of lifestyle factors characterized by lack of smoking, normal body mass index (BMI), vigorous physical activity, and adherence to a Mediterranean diet.[134] It found a ‘healthy’ lifestyle was associated with lower mortality in patients with IBD. Similarly, obesity appears to play an important role in inflammation and in response to medication. For instance, a recent prospective study identified patients with greater intra-abdominal visceral adiposity were less likely to respond to biologic therapies than non-obese patients.[146] However, while lifestyle factors may play a role in disease inflammation and are potentially modifiable, well-designed studies that examine the efficacy of lifestyle interventions on disease outcomes are lacking.

To address these gaps, it will be necessary to conduct prospective studies of combinations of advanced therapies in patients with disease unresponsive to any single therapeutic. It will also be important to determine the variation in efficacy of dietary therapies in different disease phenotypes (e.g., small bowel vs. colonic CD, perianal disease, and fistulizing disease), and identify the role of diet as adjunctive therapy during advanced therapy induction and as salvage therapy during the loss of treatment response. It is also important to develop culturally tailored anti-inflammatory diets that represent the diverse communities living with IBD. Ultimately, it will be important to conduct prospective trials which evaluate the effect of exclusion of food additives and emulsifiers on IBD inflammation. In addition to treatment of IBD, it is also important to evaluate the efficacy and optimal use of nutritional pre-habilitation on improvement of post-operative Crohn's disease outcomes. Additionally, well-designed prospective studies are needed to evaluate the effect of lifestyle modifications such as stress reduction and an increase in physical activity on disease activity, and to determine the effect of weight loss, including medications that aid with weight loss, on disease response to medication therapies.

Conclusion

Substantive progress has been made in clinical research since the previous *Challenges in IBD Research 2019*. Despite this progress, important gaps in the evidence remain, and the generalizability of the published evidence remains limited. Comparative effectiveness and safety studies are needed, particularly with newer therapies, and as applied to underrepresented populations. Research is needed to address effectiveness and safety of therapeutic approaches for subpopulations of patients with IBD who often are underrepresented in clinical trials. More evidence is needed in specific populations such as patients from racial and ethnic minorities, young children and elderly patients. Several disease phenotypes are also under-researched, including patients with limited proctitis, isolated proximal small bowel disease, those with ostomies

and J-pouches, and those with perianal and intra-abdominal fistulizing disease. Inclusion of these patients in clinical trials is crucial, but it is equally important to report subgroup results and disaggregate reporting by patient age groups. While it may be infeasible to answer all questions through clinical trials, creative approaches to research using real world data and statistical methods such as network meta-analyses can provide important information to supplement clinical trial data.

To address these important research goals over the next five years, the following should be considered:

1. Design trials to include under-researched phenotypes of disease.
2. Efforts should be made to increase inclusiveness of participants in trials by engaging underrepresented patient groups.
3. Study results should be reported with inclusion of details disaggregated by age, and disease phenotype to enable determining differential impact across these patient groups.
4. Make the most of existing data sources using data registries such as SPARC, CAPTURE, QORUS, SIRQC, and administrative databases to conduct large-scale studies of real-world data to answer questions that cannot feasibly be answered in clinical trials.
5. Increase the use of novel trial designs to facilitate pragmatic research.

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