Medical Nutrition Meeting

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CROHN'S & COLITIS FOUNDATION

Abstract

Management of inflammatory bowel disease (IBD) requires a multidisciplinary collaboration that integrates medical nutrition into the therapeutic regimen, as recommended by guidelines and supported by research. While pharmacotherapy forms the cornerstone of IBD management in the United States (US), medical nutrition therapy (MNT) is often overlooked. Despite its benefits, MNT remains inaccessible to patients in the US due to near-absent insurance coverage of the required nutritional formulas. Legislative efforts to mandate coverage have repeatedly failed due to various barriers. To address these challenges, a panel of experts was convened ahead of the 2025 European Crohn's and Colitis Organisation's (ECCO) annual meeting in Berlin, Germany to discuss the details of these challenges and develop a road map for future coverage. The findings from this meeting are presented in this paper along with action items for research and policy initiatives.

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Contents

List of Abbreviations

AGA - American Gastroenterological Association

AuSPEN - Australasian Society of Parenteral and Enteral Nutrition

CBER - Center for Biologics Evaluation and Research

CD - Crohn's Disease

CD-TREAT - Crohn's Disease Treatment with EATing

CDED - Crohn's Disease Exclusion Diet

CDER - Center for Drug Evaluation and Research

CFSAN - Center for Food Safety and Applied Nutrition

CRP - C-Reactive Protein

DSHEA - Dietary Supplement, Health and Education Act

ECCO - European Crohn's and Colitis Organisation

EEN - Exclusive Enteral Nutrition

EFCCA - European Federation of Crohn's & Ulcerative Colitis Associations

EN - Enteral Nutrition

ESPEN - European Society for Clinical Nutrition and Metabolism

ESR - Erythrocyte Sedimentation Rate

FDA - Food and Drug Administration

FSAs - Flexible Spending Accounts

GI – Gastrointestinal

Half ED – Half Elemental Diet

HFP - Human Foods Program

HRAs - Health Reimbursement Arrangements

IBD - Inflammatory Bowel Disease

IFN - Interferon

IL - Interleukin

IRS - Internal Revenue Service

JSGE - Japanese Society of Gastroenterology

MD - Mediterranean Diet

MNT - Medical Nutrition Therapy

MSA - Medical Savings Accounts

NF-κβ - Nuclear Factor Kappa B

NICE - National Institute for Health and Care Excellence

NORD - National Organization of Rare Disorders

PCDAI - Pediatric Crohn's Disease Activity Index

PEN - Partial Enteral Nutrition

QALYs - Quality Adjusted Life Years

SCD - Specific Carbohydrate Diet

T&H - Tasty and Healthy

TNF - Tumor Necrosis Factor

UC - Ulcerative Colitis

wPCDAI - weighted Pediatric Crohn's Disease Activity Index

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Overview of Medical Nutrition in Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) encompasses a spectrum of chronic inflammatory conditions, primarily Crohn's disease (CD) and ulcerative colitis (UC), which affect the gastrointestinal (GI) tract. Crohn's disease can involve any segment of the GI tract from the oral cavity to the anus, whereas UC is predominantly confined to the colon. IBD affects approximately 3 million individuals in the United States, representing a prevalence of about 1.3% of the population, with incidence rates continuing to escalate globally.

Despite the absence of a definitive cure for IBD, its management necessitates a comprehensive multidisciplinary approach, integrating medical, nutritional, psychological, and surgical interventions. In the United States, pharmacotherapy constitutes the cornerstone of IBD management, yielding significant clinical efficacy but sometimes accompanied by adverse effects. Conversely, nutritional therapy is generally well-tolerated and offers clinical benefits. This technical overview will delineate the role of diet in the pathogenesis of IBD, the specific nutritional requirements of patients with IBD, the concept of medical nutrition, and its application as a therapeutic modality in IBD management.

Diet and IBD Pathogenesis

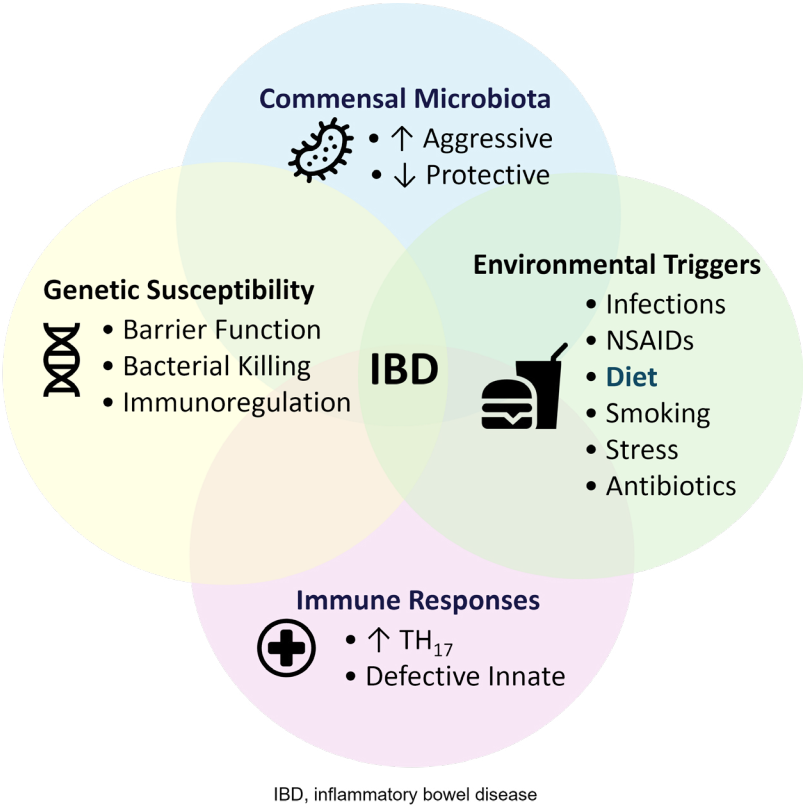


FIGURE 1. Multifactorial Pathogenesis of IBD

The pathogenesis of IBD is attributed to a complex interplay of factors, including a dysbiotic microbiome, an immune system predisposed to inflammation, genetic susceptibility (with over 200 implicated genes), disruption of the mucosal barrier, and various environmental triggers (**Figure 1**).[1,2] Diet, an environmental factor, significantly influences the microbiome and immune response. Studies indicate diets rich in fruits, vegetables, and omega-3 fatty acids, and low in omega-6 fatty acids, confer a protective effect against IBD development.[3]

Conversely, the consumption of ultra-processed foods, dietary emulsifiers (eg, carboxymethylcellulose), and preservatives is hypothesized to elevate IBD risk.[4] The mechanistic link between diet and IBD is proposed to involve dietary impacts on the microbiome, GI tract barrier integrity, and host immune function. A healthy GI tract is characterized by an intact mucosal barrier and a quiescent immune system. In contrast, an IBD-affected GI tract exhibits dysbiosis, reduced microbial diversity, diminished butyrate levels, a compromised mucosal barrier, infiltration by pathogenic bacteria, impaired bacterial clearance, and chronic inflammation.[1]

Nutritional Needs of Patients with IBD

Patients with inflammatory bowel disease (IBD) exhibit distinct nutritional requirements, with up to 85% experiencing malnutrition during their disease course.[5,6] This is particularly pronounced in patients with CD and those with active disease. Malnutrition drives up energy requirements, possibly reduces oral intake (due to a feeling of fullness from presence of strictures), and promotes excessive caloric loss from malabsorption and diarrhea.[7]

Vitamin, mineral, and caloric deficiencies are common in patients with IBD. Up to a third will experience iron-deficiency anemia, patients with ileal disease may have vitamin B12 deficiency, and vitamin D deficiency is common in IBD.[6] Pediatric patients are especially vulnerable, often experiencing linear growth stunting due to caloric deficits.[8]

Malnutrition in patients with IBD is associated with several adverse clinical outcomes, including higher hospitalization rates, increased need for non-elective surgeries, prolonged hospital stays, severe infections, development of venous thromboembolism, more frequent and severe surgical complications, and elevated mortality.

Medical Nutrition in IBD: What is it?

Medical nutrition in IBD refers to a liquid formulation that is consumed orally or administered via an enteral tube by a patient. There are a variety of formulas, including elemental, partially hydrolyzed/semi-elemental, and whole protein (polymeric).

The US National Defense Authorization Act (NDAA) of 2017 defines medical foods as a specialty formula or processed product for oral or enteral intake intended for

dietary management of patients who, due to a chronic medical condition such as IBD, cannot obtain all their nutrition from a whole-food diet alone. Medical nutrition is used under active and ongoing medical supervision, which includes in-home consumption/administration.[9] The Orphan Drug Act by the FDA defines medical nutrition as "a food that is formulated to be consumed or administered enterally under the supervision of a physician and is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."[10] For the purposes of this discussion, medical nutrition does not include whole foods and supplements, such as vitamins.

TABLE 1: Three Phases of the Crohn's Disease Exclusion Diet (CDED)

Phase	Duration	Description
Phase 1	Weeks 1 to 6	50% of calories from **Formula** 50% of calories from **Whole Foods**
Phase 2	Weeks 7 to 12	25% of calories from **Formula** 75% of calories from **Whole Foods**
Phase 3	Weeks 12+	100% of calories from **Whole, Fresh Foods** Preservatives, emulsifiers, and artificial ingredients ***excluded***

These formulas are prescribed for IBD as either exclusive enteral nutrition (EEN) or partial enteral nutrition (PEN) therapy. The EEN therapy is the use of medical nutrition as 100% of a patient's caloric and nutritional needs. This restrictive method excludes all solid food and is usually used for a duration of 6 to 8 weeks. The formula is taken orally or administered via an enteral feeding tube. To improve adherence, guidelines recommend using polymeric formula because of improved palatability and similar efficacy to other formulations.[7]

The PEN therapy is the use of enteral nutrition for less than 100% of a patient's calories. For PEN to be effective, it needs to constitute between 25% to 50% or >50% of the total caloric intake.[11] The PEN therapy has several applications in IBD. It is often used following EEN therapy or in conjunction with a whole-foods diet, such as the Crohn's Disease Exclusion Diet (CDED) with which it has been extensively studied.[12] The CDED diet is a 3-phase (**Table 1**) exclusion diet that focuses on avoiding foods and additives that may adversely impact the microbiome and compromise the integrity of the gut barrier, and it incorporates foods from high-quality sources, including low-fat animal proteins, plant-based fats, fruits, vegetables, resistant starches, and fresh whole foods.[13]

Application of Medical Nutrition in IBD Induction of Remission

The EEN therapy can be used to induce remission in active mild-to-moderate luminal CD, and has demonstrated similar or superior effectiveness to corticosteroids as an induction

strategy in pediatric CD.[14,15] A retrospective review of 127 patient records demonstrated that EEN induction therapy resulted in early remission and was associated with long-term avoidance of steroid use without increased utilization of biologic or surgical therapy.[16] The PEN therapy, when used in combination with CDED, has also been shown to induce remission in CD.[12]

The EEN therapy is recommended by international guidelines as first-line therapy for the induction of remission in Crohn's disease (**Table 2**), and for the management of inflammation, maintenance of remission, and/or the treatment of malnutrition due to IBD.[17,18,19,20,21,22,23,24] However, EEN use in the US is limited due to challenges with patient access.

Table 2: Guideline Recommendations on Medical Nutrition Therapy (MNT) in Crohn's Disease (CD)

British Society of Gastroenterology (BSGE) "We suggest that Exclusive Enteral Nutrition (EEN) may be used to induce remission in mild-to-moderate Crohn's disease patients where avoidance of corticosteroid is desired, and in those who are motivated to adhere strictly to EEN for up to 8 weeks"[17]
European Society for Clinical Nutrition and Metabolism (ESPEN) "Exclusive EN is effective and can be recommended as the first line of treatment to induce remission in children and adolescents with mild active CD."[18]
American Gastroenterological Association (AGA) "Exclusive enteral nutrition using liquid nutrition formulations is an effective therapy for induction of clinical remission and endoscopic response in Crohn's disease, with stronger evidence in children than adults. Exclusive enteral nutrition may be considered as a steroid-sparing bridge therapy for patients with Crohn's disease."[19]
Japanese Society of Gastroenterology (JSGE) • "Enteral nutrition is an effective remission-inducing therapy for active CD. Enteral nutrition therapy is safe, but acceptance of the treatment can be difficult. • Home enteral nutrition is effective in maintaining the remission of CD."[20]
Australasian Society of Parenteral and Enteral Nutrition (AuSPEN) "EEN is likely to be as effective as corticosteroids for remission induction in adults with CD who are able to tolerate EEN therapy"[21]
European Crohn's and Colitis Organisation - European Society for Paediatric Gastroenterology Hepatology and Nutrition (ECCO-ESPGHAN) "In children with active luminal CD, dietary therapy with exclusive enteral nutrition [EEN] is recommended as first line for induction of remission."[22]
National Institute for Health and Care Excellence (UK-NICE) "Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for: • Children in whom there is concern about growth or side effects[23] • Young people in whom there is concern about growth."[24]

Maintenance of Remission

The PEN therapy is used to improve the maintenance of remission, particularly for patients with CD and patients on biologics.[25] A meta-analysis of 429 patients evaluated the safety and efficacy of PEN as maintenance therapy in CD. Those receiving PEN had a significantly lower clinical relapse rate at 0.5 to 2 years versus those who were not receiving PEN. The PEN patient group also had a higher rate of clinical remission maintenance. Adverse event rates were similar between groups.[25]

Preventing and Managing Loss of Response to Biologics

Enteral nutrition has been shown to help prevent the loss of response to biologics. A retrospective observational study of patients with CD experiencing loss of response to biologics compared the efficacy of PEN + escalated biologic therapy versus escalated biologic therapy alone. The combination treatment arm was associated with a higher rate of steroid-free clinical remission at 24 weeks, greater transmural response rates, and improved nutritional status. Results suggest PEN is an efficacious add-on therapy to biologics in patients with refractory or difficult-to-treat CD.[26]

Another study of 21 patients examined the utility of PEN + CDED as a treatment strategy in children and adults with loss of response to infliximab or adalimumab. Nutrition therapy resulted in significant improvements in baseline Harvey Bradshaw Index scores, mean C-reactive protein, and mean albumin levels. Dietary therapy in this group was demonstrated to be an efficacious salvage treatment option for induction therapy in both children and adults who have failed 1 to 2 biologics despite dose escalations and combination drug therapy use.[27]

The utility of enteral nutrition on the maintenance of remission in CD with anti-TNFα biologics was assessed in a meta-analysis of 9 studies.[28] Results demonstrated a higher rate of maintenance of remission or response in the treatment arms incorporating enteral therapy versus those only on biologics. These data provide additional evidence supporting the preventative effect enteral nutrition has on loss of response to anti-TNFs.

Adjunctive Therapy to Biologics

When used as an adjunctive therapy to biologics, patients demonstrate improved clinical outcomes.[29] A real-world retrospective study compared the use of biologics alone versus biologics with EEN in ileum-dominant CD in 97 patients. Outcomes were assessed at Weeks 16 and 52. Patients receiving the combination treatment strategy had higher clinical response and remission rates, higher endoscopic response rates, and better mucosal healing at Week 16.[30] Responses were sustained throughout Week 52 and confirmed the utility of EEN as an adjunct to biologics.

Treating Malnutrition

Medical nutrition therapy with EEN or PEN is recommended as first-line treatment by ESPEN guidelines when a patient with IBD is experiencing malnutrition.[18] A study of 18

newly diagnosed pediatric patients with CD evaluated the utility of EEN. By the end of the 52-week study, the children had a significant increase in bone mineral density from baseline and improvement in nutritional status were observed.[31]

While EEN cannot yet be recommended in UC as an adjunct to the standard of care,[32] enteral nutrition may have a role in the treatment of malnutrition due to severe UC.

Perioperative Management

Guidelines recommend nutritional assessment prior to a planned IBD surgery and, if malnutrition is detected, the surgery should be postponed for 1 to 2 weeks and intensive medical nutrition therapy with EEN or PEN should be initiated.[18] Presurgical malnutrition is an independent risk factor for postoperative complications.[18] Perioperative nutritional management with enteral nutrition has shown to reduce the rate of postsurgical infectious complication, hospital stay, and costs.[18]

Despite the established benefits of enteral therapy in IBD, patients in the US have unique challenges to accessing formulas. This paper will explore the barriers to access and outline evidence-based and expert-guided action items to facilitate change and improve access for patients.

United States: Current and Future State of Medical Nutrition for IBD

Medical nutrition therapy (MNT) is available to patients globally, but it is not covered in the United States (US) by many private and most public insurers, making treatment uniquely inaccessible to US patients despite market availability. Since 2017, patient access to MNT has been a legislative priority for the Crohn's and Colitis Foundation (henceforth, "Foundation"), but legislative efforts have failed at both the state and federal levels.

Barriers to Access and Coverage

Legislative Barriers

Legislative failure can be contributed to a multitude of factors, most of which stem from a lack of education, data, or uniform lexicon. Government bodies have repeatedly blocked legislation promoting MNT, citing fiscal impact as the primary barrier.[33,34] Economic analyses performed by legislative committees have often omitted the cost savings associated with MNT, such as disease control, reduce surgical interventions and complications, reduced hospital stays, and the like.[35,36] Legislative efforts have focused on healthcare mandates on insurers to include MNT coverage for IBD and other specified metabolic disorders. Insurers have viewed these mandates as added costs, conflate coverage of MNT with the coverage of whole foods and vitamin/mineral supplements, and neglect the long-term associated cost-savings. Because of this, insurers have repeatedly opposed legislation, stating that the mandate will substantially increase their enrollees' plan premiums, increase overall healthcare costs to their members, and make healthcare less affordable for everyone. Absent economic analyses demonstrating cost savings legislation has either been stalled or blocked year-over-year.

Insurance Barriers

Because insurance plans are annual plans, policies that impact long-term results are often neglected. Member turnover in a plan, which is estimated to be about 20%, reduces insurers' incentive to invest in preventative care or benefits that will accrue over a longer time horizon. However, there is already a paradigm in place when it comes to long-term benefit accrual: Insurers will cover other preventative health measures with benefits that are accrued over a lifetime, such as vaccines, preventative care visits, and age-appropriate healthcare screening, such as routine mammograms and colonoscopies for healthy individuals. Investing in long-term health outcomes, despite substantial short-term turnover rates, can be cost effective, especially as 80% of an insurer's plan enrollees will remain, 32% return within 5 years, and 47% re-enroll within 10 years.

Provider-level Barriers

Globally, MNT is used as the primary means of induction therapy for mild-to-moderate CD and is recommended by international guidelines (**Table 2**). However, due to its inaccessibility in the US, American providers do not consider it as a primary therapy for

eligible patients. This has led to very low utilization, guideline-incongruent practices, and the emergence of a knowledge gap among providers on the utility of MNT in IBD. Providers who are not educated about the utility of MNT will not be able to identify appropriate candidates for MNT, will use steroids unnecessarily in patients eligible for MNT, and will not be able to advise interested patients confidently on MNT and dietary management of IBD. Additionally, epidemiologic data in the US have shown that 42% of patients with CD are prescribed corticosteroid monotherapy as their initial treatment modality,[37] a percentage that could be smaller if MNT was commonly employed as recommended by guidelines and recognized by providers as a steroid-sparing therapy for CD.[19,20,21]

Furthermore, because of inaccessibility and lack of education, the expert panel noted that providers who do introduce MNT to patients tend to utilize self-defeating language, often discussing medical nutrition—whether it is a formula or a whole foods diet—as something that they can do if they like, expressing low confidence in its efficacy, describing it as really difficult to comply with, and not following up and monitoring adherence. Pharmaceutical therapy is almost never discussed with such a lack of certainty and confidence. If a prescriber speaks like that about any treatment option, a patient will never take it seriously. Rather, MNT *is* therapy and there is a prescribed way to take it. Providers need education in order to package it in language that promotes its role as medicine.

History of Legislative Efforts by the Foundation and Other Non-profit Organizations

Coalition Formation

In an effort to impact legislation, the Foundation and 49 organizations and associations representing patients with a variety of diseases and metabolic disorders in need of access to MNT formed an alliance. This included gastroenterology and IBD-focused organizations, but also those representing medical and surgical conditions of malabsorption, inborn errors of metabolism and conditions on the recommended uniform screening panel (RUSP), IgE and non-IgE-mediated food allergies, and inflammatory and immune-mediated conditions of the alimentary tract. Widening the scope of the coalition was done to increase the number of impacted individuals, broaden support, and maintain close ties with partner organizations for current and future legislative collaborations. Together, the associations formed The Patients and Providers for Medical Nutrition Equity Coalition.

Medical Nutrition Equity Act

In 2017, the Coalition worked with federal legislators to introduce the Medical Nutrition Equity Act (MNEA) to Congress.[38,39] The act was reintroduced in 2019, 2021, and 2023 by law makers representing the states of Massachusetts, Pennsylvania, and Maryland.[40,41,42,43] In the House of Representatives, the MNEA of 2023 was cosponsored by 15 Democrats and 2 Republicans. The act was largely ignored by Congress, with the latest action being taken on December 17, 2024, where it was referred to the Subcommittee on Health, where it has not received attention. The Foundation and Coalition is looking to reintroduce the bill again in 2025.

State Pilots

The Coalition also commissioned a market assessment in 2017 to ascertain states that may have a mandate already in place for coverage. The assessment revealed that only 2 states appeared to have mandates, but MNT continued to be inaccessible. MNT was not being provided by insurers and most people were not aware of it.

Massachusetts

Massachusetts was one of the states with a mandate for the coverage of enteral formulas for IBD and other specified diagnoses without mention of the route of administration.[44] Insurers overwhelmingly self-reported compliance with the law. On this basis, a bill was introduced into the Massachusetts legislature in 2017 to extend insurance coverage from just "malabsorption caused by Crohn's disease" to "Crohn's disease" more broadly and would cover both oral and tube feedings. The bill would not impact federal and state funded plans. A fiscal impact evaluation showed minimal increase in monthly health premiums for plan members.[35] Despite favorable review, the bill was not enacted, with opposition stating that fully insured Massachusetts residents already have access to this level of coverage. The bill was reintroduced in 2019, 2021, and 2023, with the foundation becoming active on it in 2023 and incorporating the patient voice into the effort. [45,46,47,48] The bill was reintroduced every 2 years, and plans are in place for reintroduction in 2025.

California

In 2023, the Foundation authored a bill in California requiring coverage for MNT for the treatment of a broad spectrum of chronic digestive diseases and inherited metabolic disorders, including IBD.[49] Under the bill, all patients in need of MNT would receive it. After unanimously passing both legislative chambers, the bill was vetoed by the governor due to potential cost implications.[33]

In 2024, the opposite strategy was employed. The Foundation authored a streamlined bill that restricted MNT to pediatric digestive diseases. Restricting the population was a cost containment strategy. If the cost barrier could be overcome and the bill is enacted, data could then be generated to demonstrate cost effectiveness and be used as a basis to expand coverage in the future. Unfortunately, the bill did not pass the second chamber due to financial difficulties encountered by the state during that time.

Creating a Mandate

Insurance coverage in the United States is diverse and each category of coverage is regulated by a different government entity. **Figure 2** displays the demographic distribution of insurance coverage in the United States based on data from the 2020 Census.[50] Fifty-four percent of Americans are provided insurance coverage by an employer or union. Medicare, a federal entitlement program for citizens aged 65 years or older and qualifying individuals with specified long-term disabilities, provides coverage for 19% of Americans. Medicaid, a state-administered program for low-income individuals, including

the Children's Health Insurance Program (CHIP), covers 19% of Americans. Ten percent of Americans purchase individual health plans directly. Three percent of Americans receive health plans through the military for active or retired duty members and their families. Pursuing a legislative mandate would impact patients irrespective of their insurance provider, however, it will require a bill movement through 5 different legislative committees.

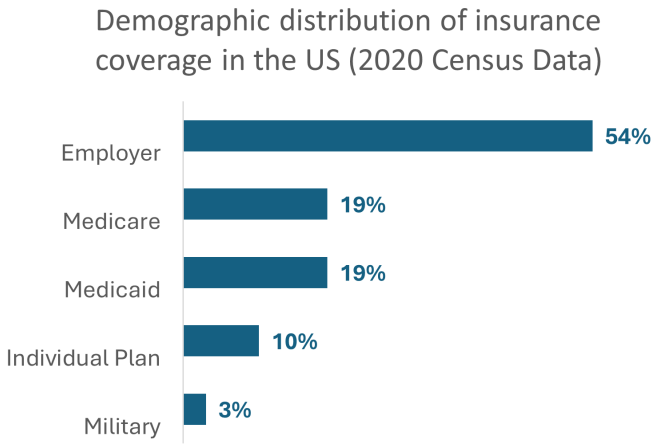


FIGURE 2. Demographic Distribution of Insurance Coverage in the US (2020 Census Data)

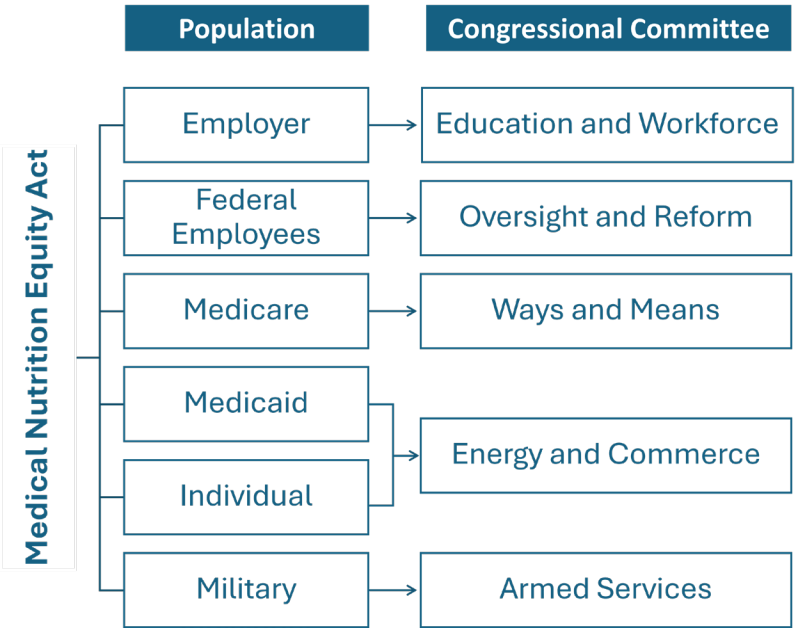


FIGURE 3. Congressional Committees Involved in the Review and Approval of the Medical Nutrition Equity Act

To create a mandate, a bill must be introduced into either the House of Representatives or the Senate. Historically, the Foundation has introduced bills simultaneously to both branches of Congress to expedite the process. In both the House and Senate, the bill goes through multiple committees and then enters the floor for a debate and votes. If approved, they both then enter into conference, where they are reconciled based on the decisions of the 2 legislative bodies. The bill then goes to the president for enactment or veto.

It can take years for a bill to become law, and many are not successful. In the 118th Congress (2023 to 2025), 19,315 bills were introduced and only 614 (3%) were enacted, despite most requiring approval of just 1 or 2 committees.[51] Because different government entities regulate healthcare coverage based on population, the MNEA must pass through 5 different committees, further complicating and prolonging the process (**Figure 3**). Despite obstacles, the Foundation and coalition members have taken steps to maximize the bill's chances of success by always incorporating bipartisan authors, providing broad patient coverage, and simultaneously introducing it into the House and Senate to accelerate timelines.

Action Items

Develop an Economic Cost Analysis

Cost has been the oft-cited barrier to legislative progress. While financial arguments have been made in favor of shorter hospital stays, faster healing, and the long-term benefits of improved outcomes, there is no data available in US patients who use formula as treatment. Evidence and data are absent because access to treatment is limited. Cost analyses performed by governmental committees focus on the immediate financial burden and do not take into consideration long-term cost savings and the impact treatment has on quality adjusted life years (QALYs). Legislation at any level, including state, cannot progress in the absence of an economic analysis:

1. Conduct a comparative effectiveness analysis in children that compares nutritional therapy to other options in inducing/maintaining remission. Incorporate a systematic review and meta-analysis in any comparative effectiveness analysis.
2. Research should include costs and outcomes analysis using QALYs comparing treatments used in the comparative effectiveness analysis.
3. Publish and share results with stakeholders, including insurers, the FDA, industry, and Congress.

Quantify Impact

There is no state-by-state mapping of who legislation is impacting. When legislators and payors think about coverage, they need to know how many people this is affecting in order to understand the financial scope of the legislation. Understanding where affected patients reside also helps develop a targeted legislative effort by soliciting lawmakers in

regions where there is greater impact and popular support. State-by-state mapping of who legislation is impacting is imperative for understanding the legislative path forward:

1. Quantify the number of constituents impacted by IBD in each state.
2. Quantify the number of people who will be impacted by medical nutrition.
3. Develop coalition partnerships at the federal and state levels from the start.

Narrow the Scope

The Coalition includes a variety of associations and organizations representing multiple disorders that benefit from MNT. Narrowing the population of focus to just IBD as a cost-control strategy alienates partner organizations, advocates, and harms future legislative collaborations. Additionally, the cause can leverage the diversity of the Coalition, as some of the specified disorders have no treatment other than MNT, making the need more urgent than in IBD where there are many evidence-based, targeted medical therapies that are viewed by legislators and payors as alternatives to MNT. However, data on MNT in pediatrics is particularly strong and may advance legislation better than a focus on the broader population:

1. Generate alignment among coalition members to narrow the scope of the bill to pediatrics.
2. Introduce revised legislation at the state and federal levels focusing on pediatrics.
3. Introduce legislation for adult coverage, subsequently as additional evidence for use in adults is generated.

Medical Nutrition for IBD in Europe: EFCCA's Role

The European Union (EU) operates under the general legal and regulatory framework of the European Commission. The 26 member states of the EU then have considerable flexibility in the application of the regulatory decisions made on the European level. This is similar to the state-by-state differences observed in the US. Healthcare decision-making is regulated under the same process.

European Guidelines

The EU has made considerable strides in the integration of MNT into IBD management. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines provide comprehensive, evidence-based guidelines for nutritional management in IBD, with an emphasis on a multidisciplinary approach to care.[18] A multidisciplinary approach to IBD care ensures that medical nutrition remains a core component of the treatment paradigm.

ESPEN and UK NICE guidelines support the use of EEN for the induction of remission in pediatric Crohn's disease (**Table 2**)—an evidence-based induction strategy that has been shown to be as efficacious as corticosteroids in this population but with less side effects.[18,24] Based on these recommendations, EEN is utilized across the EU as the primary induction method in pediatric CD.

European Whole-Foods Diets for IBD

Newer strategies incorporating whole-food diets in conjunction with PEN are also being applied on the individual member state level. One example is the Crohn's Disease-TReatment-with-EATing (CD-TREAT) diet.[52] CD-TREAT is a whole-food based diet specifically designed to induce remission in active adult and pediatric CD. Developed in Scotland, CD-TREAT focuses on reducing inflammation and promoting digestive tract healing. Studies have shown that CD-TREAT replicates the microbiome changes observed with EEN, reduces gut inflammation, is well tolerated, and potentially effective in active CD.[52] Clinical trials evaluating CD-TREAT relative to EEN are underway to ascertain the best approach to induction therapy.[53]

The IBD Anti-Inflammatory Diet (IBD-AID) is another European diet designed to reduce the inflammation and symptoms associated with IBD in patients by using whole foods to modulate the microbiome.[54] The diet consists of 5 phases, beginning with an initial restrictive stage, and then gradually reintroducing foods, as tolerated, by the patient. The IBD-AID eliminates inflammatory foods and focuses on anti-inflammatory options, including pre- and probiotic foods. A pilot study of IBD-AID demonstrated that the diet was positively correlated with an increase in *Clostridia* and *Bacteroids*, which are commonly depleted in patients with IBD.[55] A clinical practice site at the University Hospital of Heidelberg in Germany is employing this strategy as a component of a comprehensive treatment approach for patients with moderate-to-severe UC.

The Role of EFCCA-ECCO

The European Federation of Crohn's & Ulcerative Colitis Association (EFCCA) is a European organization representing 46 distinct IBD patient associations working to advocate for patients living with IBD around the world. The organization does this through networking, raising awareness, promoting advocacy, establishing solidarity, and educational empowerment.[56] Raising awareness, in particular, is a key objective and is critical for recognizing unmet patient needs and integrating them into research plans.

The organization additionally partners with medical associations to include patient representatives in clinical guideline development. The EFCCA also participates in EU-funded research projects, such as miGut-Health, which focuses on biomarker-driven nutritional interventions to prevent or reverse IBD.[57]

Ongoing Challenges

The European Crohn's and Colitis Organisation (ECCO) Guidelines for Nutrition in IBD recognize the vital role diet plays in IBD management and advocate for a multidisciplinary approach to IBD care. This requires the close collaboration of gastroenterologists, dietitians, and other members of the healthcare team. While this model represents the ideal care delivery model, it remains inaccessible to many patients because the centers providing this level of care are in major urban cities, commonly out of reach for the majority of patients with IBD.

While enteral nutrition is covered in the EU, access continues to be a problem for some patients due to member-state level differences in policies, some of which are driven by economic factors. Not every member state of the EU provides the same level of coverage and access for patients. For example, in one country, a national health system may cover 80% of a person's healthcare needs, while another may have a mixed public-private payor system, and a third may have only a private payor system.

Action Items

Educate Providers and Patients

Providers for IBD in the US are on divergent paths when it comes to MNT. Depending on the level of training, it may never be part of the clinical conversation, or it may be routinely discussed with every new diagnosis. Research and drug development exclude the patient perspective on the integration of MNT into the therapeutic regimen, which leaves clinicians to assume patient preference. However, clinicians cannot be left to insert their own biases when discussing nutritional management with patients. They need to have data-driven conversations with them. Clinicians receive a lot of education on how to position biologics, similarly, they need education on how to position MNT (Is it for perioperative management, induction, maintenance, nutritional supplementation, or an adjunctive therapy for someone with infection?). This can be achieved through Grand Rounds and

a dominant presence at medical congresses. Additionally, a multidisciplinary approach is crucial to enacting an MNT regimen, as it is impossible to treat patients with MNT without the support of a dietician:

1. Add the patient voice to the research, drug development, and approval process as it relates to incorporating medical nutrition therapy into IBD treatment regimens.
2. Continue efforts to educate healthcare professionals and patients on medical nutrition in IBD, including gaps in care and barriers to access.
3. Support a multidisciplinary approach to medical nutrition and the crucial incorporation of dieticians/nutritionists as part of the clinical care team.

Payor Insights on IBD Medical Nutrition Therapy

Payors approach healthcare from a perspective that focuses on cost-containment. When deciding on benefits and coverage, payors need data demonstrating the number of constituents impacted and the financial implications of the added benefit to their member population as a whole. Affecting approximately 2.39 million people, IBD is one of the top 5 most expensive gastroenterological conditions in the US. Annual US healthcare expenditure on IBD has explosively outpaced the steady rise in disease prevalence among the population. An analysis conducted on expenditure over the course of a decade showed an increase from $6.4 billion in 1996 to $25.4 billion in 2016, with the adjusted cost per patient nearly tripling from $5,714 to $14,033.[58] Biologics, which form the mainstay of treatment for moderate-to-severe disease, can range from $17,000 to $150,000 per person per year. However, biologics were not the main drivers of expenditure, rather, hospitalizations and emergency care were, suggesting a lack of disease control despite use of advanced medical therapies. Between 2011 to 2016, inpatient care and emergency departments visits accounted for over half the total spending... and did not abate despite increases in pharmaceutical spending from 12.8% to 19.9%. Other analyses have approximated 43% of the increase in pharmaceutical spending as attributable to biologics.[59] Per patient spending increased annually by approximately 3% from 1996 to 2013, and then by 18% per year between 2014 and 2016.[58] These data confirm the financial volatility of IBD management, the economic burden it has on society, and reinforce the need for cost-containment strategies.

Cost Containment Strategies

Insurers employ several cost containment strategies to address the rising healthcare expenditure in IBD. This includes the implementation of policies to limit or avoid add-on costs, such as unnecessary health resource utilization and duplicative interventions; the preferred use of treatment options that will replace, rather than add to, the use of another therapy; and reducing the use of expensive advanced medical therapies, such as biologics and targeted small molecules, by preferring the use of lower cost alternatives through encouraging or requiring the use of traditional disease modifying therapies, generics, and biosimilars.

Internal Policy Barriers to MNT Coverage

Over-the-Counter Status

Medical policy making at insurance companies takes into consideration what the intervention is, how it works, and whether it is cost-effective compared to the interventions already covered by the plan. Considering the cost of MNT ranges below many pharmaceutical and medical interventions ($3,600 to $36,000), it can be utilized as a cost-containment strategy, particularly if it will delay the initiation of biologics, improve outcomes, and reduce costs associated with complications, surgeries, and hospital stays. While all this may support cost-containment, the plan will likely continue to exclude MNT

from coverage due to overarching language and policies already in place. One of these policies is regarding over-the counter (OTC) products overall. The MNT formulas are OTC and plans typically exclude all OTC products from coverage. By making an exception for MNT, it establishes a paradigm for other populations to follow, leading to the eventual breakdown of the policy as a whole and a ballooning of costs. Additionally, there is a wide array of OTC products, including vitamins and supplements, and many have no demonstrated benefit or clinical trial data supporting use. Absent clinical trial data and FDA approval, insurers would have to ascertain which OTC products have medical benefit to determine coverage, a role the insurer was not meant to play and opens the door to constant policy revisions, appeals, and argumentation.

No FDA Approval

While medical foods are regulated by the FDA, they are not FDA approved. This includes health foods, diets, and formulas for which there is little or no evidence of medical benefit. Similar to OTC products, the lack of adequate clinical trial data on medical foods places the burden of ascertaining benefit on the insurer.

Addressing Internal Policy Barriers

Create a Basis for Coverage

The cost of IBD management has increased at an accelerated pace over the past few years; a basis for coverage can be created if MNT is properly positioned as a lower cost opportunity, particularly for pediatric patients. For example, studies from the UK have estimated that enteral nutrition therapy for inducing and maintaining remission in pediatric mild-to-moderate Crohn's disease is cost effective at just £20,000 per quality adjusted life years![60] Unlike in the UK and many parts of the world, payors have come to view the MNT as supportive care, and not a necessary component of a guideline-based treatment plan; it needs reframing here in the US. Insurers need data on the use of MNT as *treatment* and its impact on reducing corticosteroid use and side effects, inducing remission, and lowering overall costs. If data can demonstrate that MNT, for example, can be used as an adjunct to biosimilars to increase their safety/efficacy or reduce the need for JAK inhibitors, this would be attractive for payors as it avoids more expensive therapies and improves upon lower-cost alternatives.

Additionally, economic and financial plans intended for insurers should be focused on 1 to 2-year increments since insurance plans operate on annual schedules. If an intervention will not actualize its cost savings potential for another 20 years, that will not attract the attention of a payor. However, if there is a more immediate financial impact, like delaying the initiation of a biologic or averting side effects associated with corticosteroids, it will align better with a payor's financial planning and may receive added interest for coverage as a cost-containment strategy. While there are clinical trial data on the benefit of MNT in pediatric CD, insurers are interested in real-world utilization data and economics.

Special Benefit Designations

Setting parameters help to establish limits for coverage and may overcome the internal policy barriers on OTC and nutritional products, protecting their breakdown. This is something insurers are extremely familiar with and employ extensively. It is a time- and/or cost-restricted benefit designated for a specific treatment or set of problems. Eyeglasses are a prime example. There is a limit on the cost and number of eyeglasses a patient can receive every 1 to 2 years. Despite the limits, patients can still access eyeglasses. Health savings accounts (HSAs) operate in a similar way with time, cost, product, and service-based restrictions.

Limited or Exclusive Sourcing and Contracting

Another strategy to overcome internal barriers to OTC product coverage is to develop limited or exclusive sourcing and contracting. These are sourcing agreements that can be established between insurers and formula manufacturers. In this model, the manufacturer would provide their products to the members of a designated health plan at a lower cost guarantee for a designated timeframe (eg, a year). This is more appealing to insurers because it avoids the "open source" problem and gives them an annual estimate of expected costs.

External Policy Barriers to MNT Coverage

Adverse selection is a major issue in the insurance industry. This occurs when a single insurer adopts a higher level of coverage than its competitors, thereby attracting potentially "sicker" patients to their plan, increasing costs and liability. This is where legislation is needed. Legislation aims to create fair market conditions between insurers by setting baseline coverage requirements for health plans. States that already mandate coverage, such as Hawaii and Massachusetts, may be more amenable to legislation if an economic case can be made.

The current legislative environment has been focused on reducing costs and regulations, so a mandate may be unlikely. However, there is also an increased focus on "Food is Medicine," "Make American Healthy Again," and "Make American Children Healthy Again" that provide a favorable legislative environment for covering MNT. Insurers are now paying for prescriptions for farmers' markets, medically tailored meals (MTMs), temporary meal delivery service, and teaching people how to cook healthier meals.[61,62] This is also the case with Medicare/Medicaid.[63,64] The current environment, though focused on cost-cutting and deregulation, has opened new avenues for MNT legislation to explore.

Currently, there are no federal or state regulations precluding commercial plans from covering enteral nutrition, but insurers have not made provisions to include it, have pre-existing categorizations and systems in place that continue to exclude it, and making an exception will create a vulnerability in these systems, allow for adverse selection, and establishes a precedent for other populations to exploit, which can lead to ballooning costs over time.

Addressing External Policy Barriers

Advocate and Lobby

Policy-level initiatives need advocates to help move legislation forward. Healthcare providers, patients, and caregivers can all advocate for legislation, and formula manufacturers can lobby.

What Patients and Providers Can Do Now

There are several immediate options that patients and families in need of MNT can take advantage of now to help somewhat alleviate cost burden.

Medical Savings Accounts (MSA)

These are known as health reimbursement arrangements (HRAs), or flexible spending accounts (FSAs). The MSAs can be used to cover the costs of MNT if it is accompanied by a letter of medical necessity (LMN) from a physician. The LMN must state that the food is necessary for the treatment of the patient's IBD and should be based on a personal, preferably in-person, medical examination. The LMN should remain on file with the patient and does not need to be given to the health savings plan administrator. Because MSAs are pre-tax dollars, they are regulated by the Internal Revenue Service (IRS). If the IRS requests the LMN (eg, as part of an audit), the patient will then need to submit it. Patients can also save receipts of MSA-eligible purchases.

Tax Deductions

The IRS allows taxpayers to take deductions on medical expenses exceeding 7.5% of their adjusted gross income.[65] The IRS defines medical expenses as "*the costs of diagnosis, cure, mitigation, treatment, or prevention of disease, and for the purpose of affecting any part or function of the body. These expenses include payments for legal medical services rendered by physicians, surgeons, dentists, and other medical practitioners. They include the costs of equipment, supplies, and diagnostic devices needed for these purposes*." Health insurance premiums and the cost of transportation to receive medical care are included. Items related to general health, such as vitamins or vacations, are excluded.

Tax deductions cannot be claimed on medical expenses fully reimbursed by MSAs or on amounts contributed to MSAs.

Because tax deductions cannot be claimed on nonprescription medications, the patient must keep an LMN on file, save their receipts, and produce them if requested by the IRS.

Action Items

Create a Payor Strategy

Currently, payors view MNT as supplemental or supportive nutrition, not as an evidence-based guideline-recommended treatment strategy with cost savings potential. Insurers

also have internal barriers to implementation that may be strategically overcome with conversations around special benefit designations and contracting that may suit their specific patient populations. Once economic analyses are available, insurers need to be engaged around all forms of MNT, educated about its use as treatment, presented with data on its cost savings potential, and conversations need to be started about customizing strategies that accommodate the needs of a payor and their patient population:

1. Speak with current insurers and educate them on the issue.
2. Include smaller regional plans and self-insured employers in education and discussion efforts. They may be more open to feedback and cost data.
3. Attempt to advance coverage where there is interest.

Partner with Insurers' Charitable Foundations

Insurers do not want add-on therapy unless it will improve the current therapy or take the place of another therapy. MNT has the potential to fulfill this, but data are lacking. Funding is needed for research to explore the utilization of MNT as a combination therapy approach.

- Explore partnerships with insurers' charitable foundations to advance combination therapy research

Leverage Existing FDA Nutritional Categories

The nonprescription status of MNT is another barrier for insurers. They do not want to ascertain which OTC products have medical benefit and should be covered, and they do not want to form new categories for products. Insurers use categories already in place by the FDA, and the FDA has many different categorizations for medical foods that can be utilized when engaging with insurers.

- Utilize existing nutritional categories in place by the FDA, ensure medical nutrition therapy for IBD is included, and begin leveraging these categories to engage payors

FDA Insights and Possible Avenues to Explore

Restructuring

Historically, the FDA has not been as rigorous when dealing with issues related to medical nutrition as compared to drugs, biologics, and devices. However, the current administration's focus on nutrition and food is allowing for an unprecedented level of attention at the appropriate regulatory centers within the FDA. Historically, food has been managed by the Center for Food Safety and Applied Nutrition (CFSAN). Recent restructuring at the FDA has consolidated CFSAN, the Office of Food Policy and Response, and the Office of Regulatory Affairs into the FDA Human Foods Program (HFP). The HFP consists of 3 centers:

1. The Nutrition Center of Excellence
    a. Office of Nutrition and Food Labeling
    b. Office of Critical Foods
2. The Office of Microbiological Food Safety
3. The Office of Food Chemical Safety, Dietary Supplements, and Innovation

The newly formed Office of Critical Foods manages and regulates infant formula and medical foods, providing "analysis, planning, and direction on nutrition and food labeling initiatives and critical foods (infant formula and medical foods) for the HFP". It is responsible for the development of policies, regulations, guidance, and collaborative research projects with federal and other data partners. The Center coordinates the FDA's activities on infant formula and medical foods and promotes stakeholder collaborations and partnerships.

The Nutrition Center of Excellence

Combining infant formula and medical foods into a single office may provide a new opportunity for enteral nutrition access. Specialized infant formula in particular can serve as a familiar paradigm to guide the path forward for legislating access to enteral nutrition in IBD. Many states currently have insurance mandates requiring the coverage of medically necessary specialized infant formula for specified disorders identified upon newborn screening, such as phenylketonuria and cystic fibrosis.[66] There is an overall recognition that specialized infant formula is neither a food nor a drug but is still a medically necessary life-saving intervention. Using this familiar, high velocity product to discuss the situation more broadly to include MNT for IBD may help attract the attention of legislators. Now that they are recognized collectively under one center within the FDA may help facilitate new pathways for access.

Education and Awareness

Educating the FDA

Pharmaceutical companies spend a lot of time and energy educating the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) on their products. Nothing of a similar magnitude or nature happened at CFSAN, but these conversations need to take place and patient involvement can help. The CDER and CBER are required by law to engage patient groups in a process known as "patient-focused drug development." The patient-focused drug development program at the FDA has been an enormous success and it has been one of the areas where the FDA has been ahead of other developed regulatory systems. It would not be hard to expand this to medical nutrition. The term may need to be expanded so that it is "patient-focused healthcare development" or something entirely separate, such as "patient-focused nutritional development."

In the past, nutrition manufacturers have unsuccessfully engaged the FDA to discuss updating its approach to nutrition. In February 2024, the Healthcare Nutritional Council, an association representing medical nutrition manufacturers, approached CFSAN to modernize the definition of medical nutrition—which was first defined in 1988, outline distinctive nutritional requirements, and present a white paper on the topic.[67] While the administration was agreeable to the data, funding and interest was not available to move the project along. Considering the recent restructuring at the FDA, there is now a huge educational opportunity for third parties, particularly nutrition and food manufacturers ("Big Food"), to engage the FDA.

Open Public Hearings at FDA Advisory Committee Meetings

Advisory committees at the FDA function to provide expert insight on matters related to foods, drugs, biologics, medical devices, and tobacco products by enhancing the administration's access to expert advice. While these committees provide their recommendations, the FDA makes the final decision regarding the matter. The FDA encourages all stakeholders to take part in the decision-making process by including a minimum of 60-minutes to an open public hearing (OPH) session during advisor committee meetings. These OPH sessions are open to the general public.[68] The MNT advocates can request the FDA to convene an open public meeting on this topic.

FDA Part 15: Public Hearing Before the Commissioner

FDA Part 15 hearings are another avenue for stakeholders to present information to the FDA. These are formal, regulatory proceedings that allow members of the public to present information, data, or opinions on a specific regulatory issue.[69]

FDA Patient Listening Sessions

Members of the IBD community can request a Patient Listening Session with the FDA to voice their opinions. FDA Patient Listening Sessions are hosted by the FDA Public Engagement

Staff who serve to connect patients, caregivers, and patient organizations directly to the FDA. Here, patients are given private, informal, non-regulatory, non-binding virtual meetings with FDA staff members to share their experience, views, and needs as they relate to their health or disease. The sessions are not to be attended by industry or their representatives and are not for discussion on specific investigational products. These sessions are in collaboration with the National Organization of Rare Disorders (NORD) and the Reagan-Udall Foundation for the FDA. Summaries of the sessions are then published online.[70]

Educating Insurers Under FDAMA 114

In addition to educating the FDA, formula manufacturers can directly educate insurers as drug manufacturers commonly do. Section 114 of the Food and Drug Administration Modernization Act of 1997 (FDAMA 114) provides guidance on how drug manufacturers can liaise with third party payors to educate them on the economic value of their products when making coverage decisions.[71] Advocates and companies developing nutritional products for IBD should follow this paradigm and educate payors about the economic value of their products.

Better Quality Data Needed

When engaging the FDA on food and nutrition-related products, it is important to keep in mind the framework within which the FDA operates. The centers that evaluate drugs, biologics, and medical devices have historically received more budgetary attention than the former CFSAN, despite food science being a rigorous field of study, with peer-reviewed journals, qualified researchers, and NIH-grant funded projects. However, pharmaceuticals dominate the literature with high quality science, data, and studies, whereas much of the studies done on MNT are poorly conducted.

Much of the research talent and expertise is in pharmaceuticals. MNT professionals need training in the design and execution of high quality, rigorous, real-world studies in medical nutrition. However, there may be opportunity for nutrition experts to collaborate with pharmaceutical companies and leverage their expertise and funding to generate better data on EN as combination therapy with biologics—a very familiar term to regulators at CBER. Regulators may be more receptive to review EN in the context of combination therapy with biologics, particularly if data demonstrate improvements in efficacy and cost. However, for the FDA to regard EN as therapy, it must be submitted to the FDA with all the appropriate elements: indications and usage, dosing and administration, dosage forms and strength, contraindications, warnings and precautions, adverse reactions, interactions, use in special populations, description, pharmacology, non-clinical and clinical studies, storage and handling, and patient counseling.

There is much resistance to added costs, and while combination therapy may come with an upfront cost, it is postulated to reduce future costs. However, there is no data to confirm this.

Dietary Supplements and Qualified Health Claims

Additionally, when engaging the FDA regarding nutrition and foods, it is important to understand the entanglement between medical food, dietary supplements, and qualified health claims, and how a broken, unstandardized lexicon contributes to the confusion.

The Dietary Supplement Health and Education Act (DSHEA) of 1994 requires the FDA to regulate dietary supplements as food products.[72] Despite regulations being in place to prevent food products and dietary supplements from making drug-related claims, many manufacturers irresponsibly do with dietary supplement advertisements being nearly indistinguishable from commercials for medications to the average consumer. The products typically make poorly supported claims regarding health, are poorly manufactured, and commonly not labeled to accurately reflect their contents. Consumers generally pay out-of-pocket for them and insurers typically do not provide coverage. Medical foods will fall under this broken regulatory framework.

Moreover, when we are discussing medical nutrition and its use as treatment, the issue of a "qualified health claim" becomes pertinent. According to the FDA, a qualified health claim is one that is "supported by scientific evidence, but do[es] not meet the more rigorous 'significant scientific agreement' standard required for an authorized health claim."[73] These statements are not approved by the FDA and are required to be accompanied by a disclaimer communicating the level of scientific evidence supporting the claim. A manufacturer may petition the FDA to consider a claim based on supporting scientific evidence. If qualified, the FDA will issue a Letter of Enforcement Discretion detailing the level of scientific evidence supporting the statement and outlining factors under which it will permit the use of the claim without objection. If unqualified, the FDA will issue a letter of denial.

For example, in May 2009, the FDA issued a warning letter to General Mills for using an unauthorized health claim on its Cheerios boxes.[74] The health claim stated, *"Did you know that in just 6 weeks Cheerios can reduce bad cholesterol by an average of 4 percent? Cheerios is . . . clinically proven to lower cholesterol. A clinical study showed that eating two 1-1/2 cup servings daily of Cheerios cereal reduced bad cholesterol when eaten as part of a diet low in saturated fat and cholesterol."* The letter warned that the statement made the cereal an unapproved new drug since the claim implied the product is intended for "preventing, mitigating, and treating the disease hypercholesterolemia." The manufacturer was asked to remove the statement due to a lack of evidence. The message from the FDA was clear: If a manufacturer of a food product wants the general population to recognize the health benefits of their foods beyond basic nutrition, then the health claim needs to accurately reflect the level of evidence supporting it. Otherwise, the manufacturer will be accused of marketing an unapproved drug.

Currently, the FDA has no incentive program to encourage food and nutrition manufacturers to produce better data supporting their qualified health claims. In the

past, the FDA used to assign a grade to the claims as an incentive. Unfortunately, the manufacturers stopped seeking qualified health claims from the FDA because the standard to reach a grade of "A" was unattainable. The program failed. The FDA needs to produce a method to incentivize the food and nutrition manufacturers to do better research to support their health claims.

Further complicating the issue is the broken lexicon used to describe functional foods, medical nutrition, and dietary supplementation. Different people use the same phraseologies to mean different things, creating confusion. Terms such as "light" or "healthy" are regulated terms, but they are used very loosely by manufacturers. The lexicon governing medical nutrition needs standardization, particularly if legislation is sought.

The growth of the dietary supplements and health foods market in recent years necessitates a greater level of compliance and regulation. The FDA needs proper staffing, budgeting, and partnerships with stakeholders, including researchers and disease-focused organizations and associations interested in treatment options beyond drugs, biologics, and medical devices, to address this growing issue.

Federal Coverage

When discussing legislating access to MNT, coverage under Medicare may continue to be an obstacle, particularly in light of recent tensions between the FDA and the Centers for Medicare & Medicaid Services (CMS). The single largest payor for healthcare services in the US is Medicare.[75] In the past, when the FDA approved a product, CMS would decide whether it would reimburse it. Now, CMS may question and even disagree with the science with which the FDA uses to bring a product to market, blurring the boundaries between the agencies. This has implications when applied to reimbursing medical nutrition, functional foods, and dietary supplements.

Is FDA Involvement Required?

Involving the FDA in improving access to MNT has its advantages and disadvantages. The FDA adds a layer of delay, cost, and confusion. However, removing the FDA from the conversation telegraphs distrust to payors, physicians, patients, legislators, and other stakeholders. If MNT is to be treated as serious science with serious healthcare opportunities, it needs to be regulated through the typical channels. Additionally, CMS and third-party payors look to the FDA for its categorization of healthcare products to determine coverage (eg, Cell and Gene Therapy, Biologics, Biosimilars, etc); payors do not want to invent categories on their own.

The current political environment may be very receptive to lobbying the Department of Health and Human Services for nutrition-related products. However, this should not impede approaching payors concurrently and independently.

Challenges and Opportunities in Unprecedented Times

The year-over-year challenges of securing coverage for enteral nutrition in the US is entangled by both opportunities and challenges presented by the current political environment. The Secretary of the Department of Health and Human Services ("Secretary") has shifted the department's priorities to nutrition, including the establishment of the "Make America Healthy Again" commission and a focused revamping of the FDA's nutrition programs.

On March 27, 2025, the US federal government announced mass workforce reductions to the Department of Health and Human Services (HHS), affecting the Food and Drug Administration (FDA), National Institutes of Health (NIH), and Centers for Disease Control and Prevention (CDC).[76,77] The Secretary commented that the restructuring is in line with his strategic priority to refocus the agency to align with his core mission of "reversing the chronic disease epidemic" and emphasizing prevention. The restructuring will include the development of a new agency, Administration for a Healthy America (AHA), which will focus on chronic disease prevention. According to the HHS press release, this will be done by focusing on "safe, wholesome food, clean water, and the elimination of environmental toxins." This is the first time nutrition and food are at the center of the focus for the FDA. While challenges abound, these changes offer new avenues and opportunities to revisit legislation promoting enteral nutrition coverage and policies that focus on food as medicine that have failed in the past.

Action Items

Standardize the Medical Nutrition Lexicon

What is medical nutrition therapy? There are a lot of terms used to discuss it, and they mean different things to different people. Advocates for MNT will struggle with legislators and regulators if a common lexicon is not established. The medical nutrition lexicon needs to be standardized.

Modernize the Interpretation of the Orphan Drug Act

The definition of "medical nutrition" was established by an amendment to the Orphan Drug Act over 30 years ago. Yet, some key terms remain undefined. For example, the statutory definition of a medical food states that it is "intended for the specific dietary management of a disease or condition" yet the regulatory definition states it is "intended for the dietary management of a patient" since "food" is excluded from claiming a role in the prevention, treatment, mitigation, or cure of disease—which would define it as a drug. In addition, the interpretation of the phrase "distinctive nutritional requirements" has been the subject of ongoing debate, and has remained without an explicit definition by the FDA, leaving the administration open to criticism that it has been too narrow with its interpretation.[67] There needs to be a modernized interpretation and clarification of the Orphan Drug Act as it relates to medical nutrition.

Take Advantage of the Current Administration's "Food is Medicine" Approach

For the first time since its inception, HHS is emphasizing nutrition, food safety, and food as medicine—particularly regarding its role in disease prevention and treatment—and has restructured the department to reflect these goals. While many legislative efforts have failed in the past, a reintroduction of these efforts may be especially successful in this new environment. Advocates of MNT in IBD need to take advantage of the current administration's "Food is Medicine" approach and continue legislative efforts despite past failures.

Educate Members at the Office of Critical Foods

Regulators at the centers that govern nutrition are not accustomed to meeting with patients, researchers, and advocates for nutrition policy as the members of CDER and CBER are. But, if medical nutrition is to be pursued as therapy, these centers, such as the Office of Critical Foods, need to be approached in the same way pharmaceutical manufactures approach, engage, and educate their respective regulators at the FDA.

Engage CDER and CBER if a Combination Therapy Strategy is Adopted

The CDER and CBER regulators excel in public engagement. The attention of regulators at CDER/CBER can be engaged if MNT stakeholders are able to develop an evidence-based combination therapy strategy that integrates drugs/biologics with MNT.

Generate Real-World Evidence on MNT in IBD

While there are a lot of clinical data supporting MNT in IBD, particularly pediatric CD, there are no cost effectiveness data or real-world studies from the US demonstrating long-term cost reductions due to, for example, reduced disease severity, averted hospitalizations, decreased surgical interventions, reduced emergency department utilization, and the like. Studies like this have recently emerged for anti-TNF therapeutic drug monitoring in IBD, justifying the upfront increased cost through demonstrated long-term cost savings.[78,79,80] Similar real-world evidence needs to be generated for MNT to support claims of long-term cost effectiveness. While some international studies have demonstrated cost effectiveness of MNT in IBD,[60] they do not compensate for the lack of domestic data. Anything demonstrated internationally will need to be replicated domestically for regulatory consideration.

Develop Best Practices for Clinical Trials and Harmonize Endpoints

Many of the trials in MNT are poorly conducted, particularly in comparison to data generated by pharmaceutical manufacturers. Best practices for clinical trials in MNT need to be developed and adhered to:

1. Create best practices for conducting clinical trials in MNT.
2. Standardize endpoints and measurements used in medical nutrition research to ensure consistency across trials.

Define the Parameters of Medical Nutrition as Therapy

Any pharmaceutical product presented to the FDA for evaluation needs to have defined parameters regarding its indications and usage, dosing and administration, dosage forms and strength, contraindications, warnings and precautions, adverse reactions, interactions, use in special populations, description, pharmacology, non-clinical and clinical studies, storage and handling, and patient counseling. Additionally, pharmacokinetic and pharmacodynamic studies need to be completed to inform dosing, which are costly to conduct. However, these parameters need to be defined for MNT in IBD if the intention is to position the formulas as pharmaceutical products.

Appendix 1: Scientific Rationale for Enteral Therapy in Managing IBD

The effectiveness of EEN on inflammation and disease activity in Crohn's disease may be mechanistically mediated through the microbiome, metabolome, and immune function—but it is an extraordinarily challenging mechanism to elucidate due to the impact diet has on all these variables, some of which may be irrelevant to disease activity and inflammation (**Figure 4**). Studies have observed that a decline in disease activity and remission are associated with reduced inflammation and changes in the gut microbiome, which then impacts immune signaling—resulting in a bidirectional relationship. There may also be undiscovered mechanisms beyond these variables that also impact disease activity and inflammation, making studying the interaction particularly difficult.

EEN is thought to quelle disease activity in IBD by altering microbiota, modulating the luminal metabolome, impacting the intestinal epithelium, improving nutritional status, minimizing xenobiotic exposure, and having a direct effect on immune events, among others.[81]

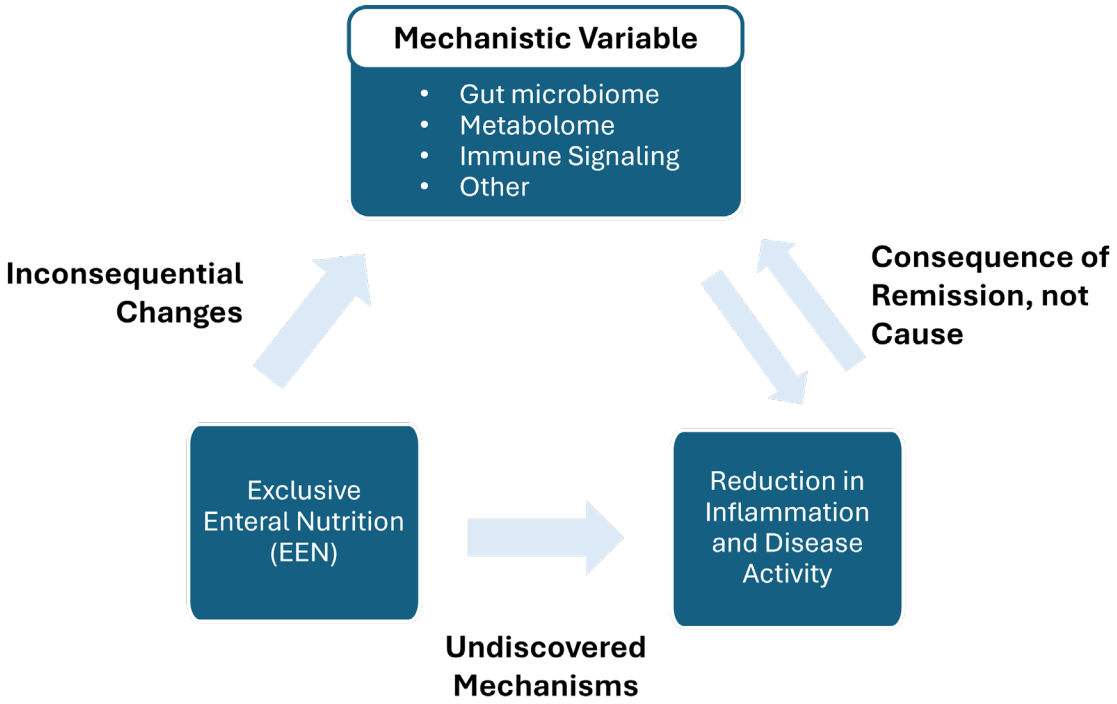


FIGURE 4. Challenges of Investigating the Mechanisms of EEN Effectiveness on IBD Disease Activity and Inflammation

The Microbiome

A study conducted in 2005 was aimed to assess the impact of enteral formulas on fecal microbiota and short chain fatty acids in 10 healthy volunteers.[82] Subjects were asked to

eat a normal diet for 14 days to obtain a baseline, then they consumed enteral formula exclusively for a 14-day period, then resumed a normal diet for a 6-week washout period, and finally were given enteral formula exclusively for another 14-day period. During the first enteral feeding period, subjects consumed either a standard, fiber and fructooligosaccharide (FOS)-free formula or a formula supplemented with fiber and FOS and then crossed over to the other formula option after the 6-week washout period. Consumption of standard formula resulted in large reductions in the metabolome, including reduced acetate, propionate, and butyrate concentrations in subject feces. The total cell count and total bacteria in feces were also reduced with *Bacteroids, Roseburia* group, *Faecalibacterium prausnitzii* group, *Ruminococci*, and *Enterobacteriaceae* particularly impacted.

Other studies have noted a dose-dependent effect of EEN on the microbiome in healthy participants. In a study of 61 healthy participants, subjects replaced 100%, 85%, 50%, or 20% of their diets with EEN. When EEN replaced 85% or more of the diet, fiber-fermenting taxa were reduced, including *Agathobacter*, *Faecalibaterium*, *Succinivibrio* and *Acidaminococcus*; and *Eubacterium*, *Actinomyces*, and *Klebsiella* populations increased. All changes were observed in a dose-dependent manner: the more the food was replaced with EN, the more change was observed in the gut microbiome.[83]

The association between EEN and the microbiome was also investigated in children with CD. Fecal samples for time periods before, during, and after EEN were collected from 23 children with CD and compared to 21 controls.[84] In the period before EEN, children with CD had lower microbial diversity than controls. During the EEN period, the microbial diversity in children with CD continued to decline and became increasingly dissimilar from the control group, despite improvements in CD. *Lactococcus* was the only taxa found to increase during EEN. Reduced microbial diversity is often associated with negative outcomes, but another study in 78 pediatric patients with CD suggests changes are patient-specific: patients will experience different EEN-related alterations in their microbiome to induce remission in CD. Results were further validated in mouse models.[85]

It has also been postulated that EEN may function by reducing the growth of potentially harmful bacteria. One study aimed to investigate the effect of the potentially harmful anaerobic segmented filamentous bacteria in a CD mouse model.[86] The study contained 3 groups (**Figure 5**). The first and third groups were fed a normal diet for 8 weeks. The second group was fed a normal diet and then started EEN at Week 7. Segmented filamentous bacteria (SFB) were introduced to all 3 groups by oral gavage at Week 8. After SFB introduction at Week 8, Group 1 continued to receive a normal diet, Group 2 continued EEN, and Group 3 was started on EEN at Week 9. Mice were sampled at Week 12 and qPCR levels and histopathology scores were assessed. After SFB introduction, high levels of histopathology were detected in the mice only receiving the normal diet (Group 1). No inflammation was developed in EEN-fed mice, regardless of whether the EEN was received before (Group 2) or after (Group 3) SFB introduction. Quantitative PCR results

demonstrated high levels of SFB in Group 1 and low levels of SFB in Groups 2 and 3. The study demonstrated that SFB easily populates the gut microbiome of mice fed normal diets but cannot populate the gut microbiome of mice fed EEN either before or after they are introduced. Analysis of fecal content and the gut epithelium by bright-field microscopy further confirmed results. The study provided evidence that EEN antagonizes SFB colonization, preventing CD development in germ-free mouse models.

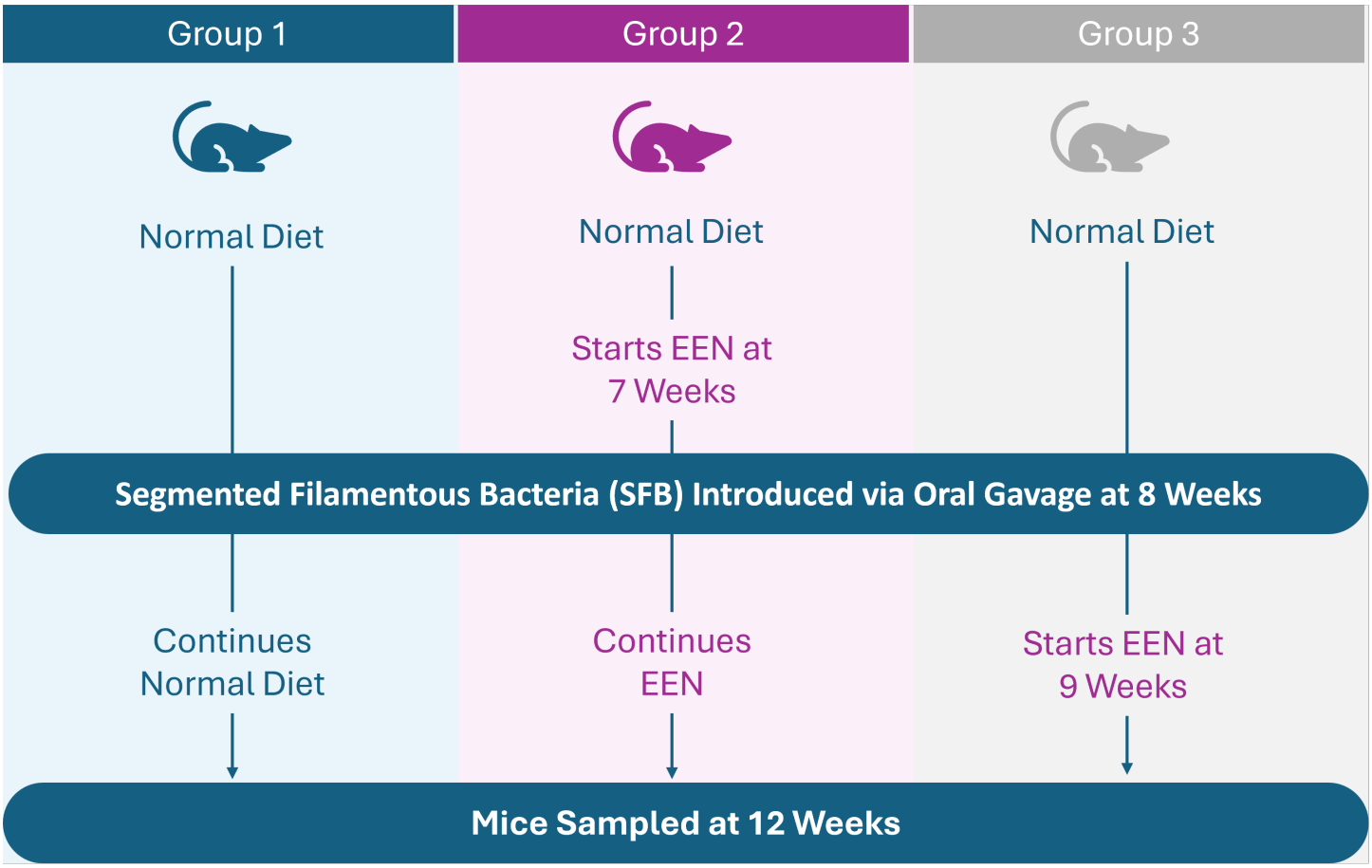


FIGURE 5. Schematic of a Preclinical Study Assessing the Effects of EEN Introduction on Harmful Bacteria (SFB) in a CD Mouse Model

Another study aimed to investigate if baseline microbiome and metabolome compositions can be used to predict response to EEN in pediatric CD was conducted.[87] Thirty-seven children were recruited and provided with pretreatment fecal samples. The children were then treated with EEN and 15 were identified as responders (fecal calprotectin <250 Qg/g). Fecal samples were collected post-treatment as well. Pretreatment fecal metabolites were assessed for EEN responders and non-responders. EEN responders were observed to have had significantly lower baseline levels of acetate, butyrate, phenylacetate, and 3-(3-hydroxyphenyl) propionic acid, with butyrate identified as the main driver of the model. Pretreatment fecal microbiota analyses demonstrated higher

levels of *Bacteroides, Lachnospiraceae, Ruminococcaceae,* and *Anaerococcus* in non-responders; *Acidaminococcus* and *Collinsella* were higher in responders. Overall, EEN responders were observed to have greater gut diversity, but their microbiome was less metabolically active.

Collectively, these studies demonstrate that EEN works through a variety of mechanisms to induce remission in IBD, some of which may be counterintuitive based on current knowledge.

The Immune System

Several studies have investigated the impact of EEN on immune markers.[88] These studies have demonstrated reductions in inflammatory cytokines and upregulation of anti-inflammatory cytokines in association with EEN (**Table 3**). However, it is uncertain if these immunologic changes were induced by EEN or if they are simply a result of the patient now being in remission.

TABLE 3. Impact of EEN on Immunological Indices

Study	Participants	Duration	Formula type	Findings
Yamamoto, et al. (2005)	n=28; adults Active disease	4 weeks	Elemental	Reduction in mucosal inflammatory cytokines Normalization in the IL-1ra : IL-1 ratio (correlated with mucosal healing)
Yamamoto, et al. (2007)	n=40; adults Clinical remission (CDAI <150)	>1 year	Polymeric (nasogastric tube overnight) + low-fat diet daytime versus No diet therapy	• Mucosal IL-1β, IL-6, and TNF-α concentrations at 12 months: significantly increased with time in untreated groups • No change in EEN group
Fell, et al. (2000)	n=29; children Active disease	8 weeks	Polymeric	Downregulation mucosal inflammatory cytokines In colon and ileum: • IL-8 mRNA elevated pre-EEN in colon only; reduced following treatment • Reduced Interferon-γ (IFN-γ) mRNA in ileum only • Reduction in interleukin-1β (IL-1β) mRNA in ileum and colon • 10-fold increase in TGF-β1 mRNA in ileum only
Rolandsdotter, et al. (2019)	n=6; children Active disease	6 weeks	Polymeric	Reduced overall expression mucosal cytokines No significant difference in mucosal cytokines profiles
Schwerd, et al. (2016)	n=15; children Active disease	3 weeks	Elemental or polymeric	In peripheral blood mononuclear cells: • Reduced secretion of IL-6, IL-8, IL-1β and TH1-derived IFN-γ when stimulated with bacterial ligands • Enhanced capacity of IL-10 to suppress LPS-induced IL-6 • Increased FOXP31 Treg and gut-homing TH cells expressing α4β7-integrins • In lamina propria, reduced Treg cells

Reproduced from: Melton SL, et al. *Aliment Pharmacol Ther.* 2023;57(9):932-947.

A Crohn's-like colitis rat model was used to further elucidate the relationship between EEN and immunologic changes. Rats were divided into 4 groups: Control rats fed a normal diet, control rats fed EEN, rats with CD-like colitis fed a normal diet, and rats with CD-like colitis fed EEN. Body weight was monitored and feces were collected for 7 days; macroscopic

and histologic examinations were performed upon euthanization. Differences were noted in the CD-like colitis rat models: those fed an EEN diet had less macroscopic inflammation, no IL-6 mRNA expression in mucosal samples, reduced interferon gamma, and reduced IL-17 when compared to CD-like colitis rats fed a regular diet.

Paradox

There are counterintuitive findings when it comes to the composition of EN formula and the findings described above, some of which are unexpected or paradoxical. These paradoxical findings are a reminder that continued research is needed to understand the mechanisms by which EEN functions in the treatment of CD.

Fiber

Fiber is fermented in the gut to produce butyrate, a short-chain fatty acid that helps regulate fluid and electrolyte absorption in the large intestines, regulate colonic motility, increase colonic blood flow, reduce symptoms of colitis, and may protect against colon cancer.[89,90,91] It has long been known to be exceptionally good for gut health.[92] So, it is paradoxical that the administration of EN formula, which is fiber-free, would be beneficial.

A study investigating this paradox in a mouse model.[93] In humans, loss of IL-10 or its receptor subunits is associated with pediatric IBD. The mice lacked interleukin-10; in a germ-free environment, IL-10 knockout mice typically have little to no inflammation and require exposure to select pathobionts to develop it (eg, *Enterococcus faecalis* or *Helicobacter* spp). The mice were then divided into 3 groups. The first was fed a fiber-rich diet, the second was fed a fiber-free diet, and the third was fed EEN. The group that was fed a fiber-rich diet had a reduction in mucolytic bacteria and inflammation and an increase in the thickness of their mucus layer. Those fed a fiber-free diet had an increase in inflammation, mucolytic bacteria, mucus penetrability, and total IgA. Those receiving EEN (a fiber-free product) had reduced inflammation and mucus layer thickness, and increased isobutyrate production. Isobutyrate is a branched short-chain fatty acid produced in minuscule amounts by the microbiome. The production of isobutyrate was heavily correlated with reduced inflammation.

Faecalibacterium prausnitzii

Faecalibacterium prausnitzii plays a prominent role in CD. Patients who have high concentrations of *F. prausnitzii* have a lower risk of relapse and longer periods of remission.[94]

Studies in mice have demonstrated oral administration of *F. prausnitzii* or its supernatant reduces colitis severity.[95] *In-vitro* evidence suggests the species secretes anti-inflammatory metabolites that significantly reduce IL-12 and IFN-γ production levels and increase IL-10, with supporting *in-vivo* data demonstrating inhibitory effects on NF-$\kappa\beta$ activation and IL-8 production. Yet, when patients are fed EEN in clinical trials, *F. prausnitzii* populations are reduced, as observed in a study of 15 pediatric patients with CD.[96] Fecal samples were

collected while on habitual diet and then at 4 different timepoints during EEN (at the start of EEN, at Day 15, Day 30, and at the end of EEN—approximately Day 60). Fecal bacterial metabolites, pH, microbial diversity, microbiota composition stability, and changes in 7 bacterial groups implicated in CD were analyzed and compared to controls. Results demonstrated an increase in pH and total sulfide, a decrease in butyric acid, bacterial diversity, microbiota composition stability. *F. prausnitzii* concentrations were significantly decreased following 30 days of EEN; which normally would not be considered beneficial, but people are achieving remission on EEN despite this paradox.

Emulsifiers

Ecological, animal, and cell studies have established a positive correlation between the consumption of emulsifiers and IBD development through mechanisms that promote inflammatory intestinal microbiota, disturbed mucus architecture, inflammatory pathway activation, and cell cycle disruptions.[97] Several studies have demonstrated emulsifiers affect the lumen of the gut causing alterations to the microbiome, a reduction in mucus thickness, increased intestinal permeability, and changes in tight junction protein expression change causing inflammation and colitis.[98,99]

A recent study investigated the therapeutic benefit of a low-emulsifier diet (LED) and CD in 154 participants.[100],[101] Treatment subjects followed an LED and controls followed an LED with emulsifier re-supplementation. Results indicated an LED is a nutritionally complete, safe, and feasible diet in CD. Subjects following the diet experienced an improvement in CD symptoms and were twice as likely to reach remission as controls, suggesting the diet is an effective treatment option in mild-to-moderately active CD.

Despite evidence demonstrating emulsifier consumption contributes to IBD development and a diet low in emulsifiers reduces symptoms, many EN formula contain emulsifiers to stabilize the water and fat content in the formula, prevent separation, ensure consistency in texture, improve absorption, and enhance palatability.[102,103] Many emulsifiers implicated in IBD, such as modified starch, inorganic phosphates, maltodextrin, soy lecithin, carrageenan, carboxymethyl cellulose, sucralose, and polysorbate 80, are present in EN formula yet patients continue to achieve remission despite this.[104] However, considering the current US administration's emphasis on nutrition, there may be a need to reformulate these products to facilitate legislative adoption.

Action Items

Prescribe the Formula the Patient will Take

There are many different formulas on the market for EN. Some are polymeric, others elemental amino acid-based formulas. They have different fat and carbohydrate content. Yet, despite these differences, they all elicit the same response. The best formula to give is the one the patient will take.

Consider Reverse Engineering EN Formula with Whole Foods

Adherence to a liquid diet is very difficult. Several studies have investigated whole-food diets that replicate the results achieved by EN, such as CD-TREAT and CDED. While EN is good for CD, it is not great for the microbiome since it reduces diversity and does not normalize it. Some evidence-based whole-food diets achieve the same therapeutic outcome with better adherence and a positive impact on the microbiome. A whole-foods diet may also be more easily accessible to patients than formula. The Foundation will closely monitor the ongoing research and evidence supporting whole foods and adapt strategies to ensure access and on-going education in this area of advancing science.

Consider the Development of Emulsifier-free Formula

The presence of emulsifiers may hinder legislative efforts in the current political environment, considering these artificial food additives are linked to disease—including IBD. An effort to reformulate the products may help improve future legislative progress.

Research the Mechanism of Action of EEN

There is a counterintuitive relationship between formula composition, microbiome changes, and disease control. More research is needed to understand the mechanism of action of EEN in the treatment of CD.

Appendix 2: Clinical Evidence to Support Enteral Nutrition in Crohn's Disease

Enteral nutrition formula access is a covered health benefit in Japan. This section will detail the Japanese clinical experience with EN.

Types Formulas

Enteral nutrition formulas are categorized into 3 types: elemental, semi-elemental, and polymeric (**Table 4**). Elemental formulas contain amino acids that lack antigenicity and require minimal digestion. Their fat content is very low, approximately 2% of total calories, making them less palatable and potentially impairing patient compliance. Conversely, polymeric formulas use proteins that require digestion. The polymeric formula has a higher fat content that increases palatability. In Japan, elemental formulas are commonly used for CD as they are fully absorbed with minimal digestion that reduces the burden on the affected bowel.

TABLE 4. Enteral Nutrition Formula Types and Administration

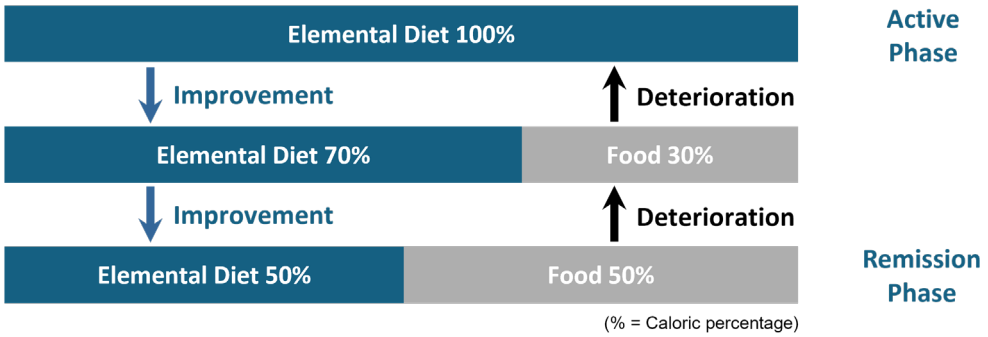
	Elemental Formula	Semi-elemental Formula	Polymeric Formula
Nitrogen Source	Free amino acids (simple, easily absorbed)	Hydrolyzed proteins or peptides (partially digested)	Partially hydrolyzed proteins (some intact proteins)
Carbohydrates	Simple sugars (eg, glucose)	Simple sugars or partially digested carbohydrates (eg, maltodextrin)	Complex carbohydrates (eg, starch)
Fat Content	2% of total calories	10% to 20% of total calories	30% to 40% of total calories

Administration

Enteral formulas are typically administered orally. Nasogastric tube feeding is an alternative option if oral administration is unfeasible due to poor palatability or if the patient has a large EEN volume requirement. For tube feedings, patients self-insert the tube before bedtime and continuously administer the formula with an infusion pump while asleep; daily activities are not restricted due to the nocturnal infusion. In Japan, the elemental formula Elental® is commonly used for patients with CD. One pack is mixed with lukewarm water to prepare 300 milliliters of formula with a 1 kcal/mL caloric density. Flavors are often added to enhance palatability. Patients are initiated on a low concentration. They are then gradually titrated up over the course of a week to reduce the risk of abdominal pain and diarrhea.

Elemental diet therapy is utilized in a stepwise approach in Japan (**Figure 6**).[105] During active CD, food intake is discontinued entirely and all calories are provided through an

EEN with elemental formula. As the disease improves and remission is achieved, 50% of calories will come from EEN, and the other 50% will come from whole food; in Japan, this is termed Half Elemental Diet (Half ED). During flare-ups, the proportion of the elemental diet is increased, while food intake is reduced.



Yamamoto T, et al. *Aliment Pharmacol Ther*. 2009;30(2):99-112.

FIGURE 6. Stepwise Elemental Diet Therapy as Applied in Japan

Clinical Impact

The impact of EEN on clinical parameters, such as mucosal inflammation and remission, has been studied in multiple clinical trials. One study recruited 28 patients with active CD and 20 healthy controls.[106] Subjects were treated with an elemental diet for 4 weeks, with mucosal biopsies obtained before and after treatment to measure mucosal cytokine concentrations. No concomitant steroid, immunosuppressant, or biologic use was allowed. Patients were also not allowed to consume any whole food or administer parenteral nutrition, except for lipid emulsions. Upon study completion, 71% of patients achieved clinical remission, with evidence of small bowel endoscopic healing and improvement in 44% and 76% of patients, respectively, with similar results observed in the large bowel (**Figure 7**). Inflammatory cytokine levels (IL-1β, IL-1RA, IL-6, IL-8, and TNF-α) in the ileum and large bowel of patients normalized upon treatment completion. EEN therapy was associated with mucosal healing, reduced mucosal cytokine production, and a restoration of balance between pro-inflammatory and anti-inflammatory cytokines as measured by an increase in the IL-1RA:IL-1β ratio.

EN has also been shown to be efficacious for maintaining remission. A clinical trial of 40 patients with quiescent CD randomized patients to an EN group (a half ED treatment that consisted of daytime low-fat meals and nocturnal nasogastric EN infusions) and a non-EN group (no dietary restrictions or nutritional formula).[107] Patients were maintained on nutritional therapy and followed for 1 year. Ileocolonoscopy was performed at baseline, 6 months, and 12 months, with biopsies obtained for cytokine assays. Upon study completion, significantly more patients in the non-EN group experienced a relapse (65%

vs 25%, *P*=0.03). Endoscopic inflammation scores and inflammatory cytokine levels were significantly higher for the non-EN group. Long-term treatment with half ED was shown to maintain remission and suppress clinical and endoscopic disease activity. Additionally, EN had a positive impact on nutritional status as observed by higher body mass index and serum albumin at 12 months, and increased caloric intake driven primarily by carbohydrates (**Figure 8**). A similar study (N=40) provided support for the efficacy of this long-term nutritional regimen on maintaining remission after surgical resection for CD (**Figure 9**),[108] with follow-up data demonstrating suppression of postoperative recurrence at 5 years without corticosteroid, immunosuppressant, or infliximab use except upon recurrence, which was much lower in the EN group (10% vs 45%, *P*=0.03).[109]

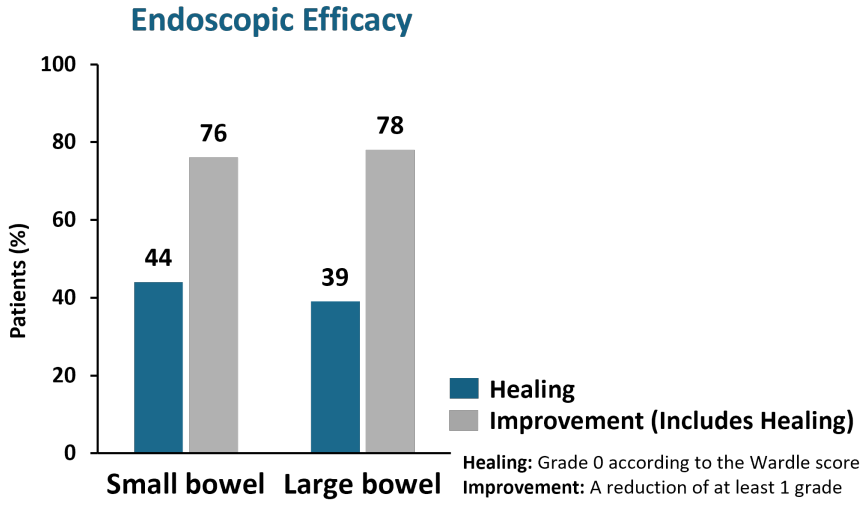


FIGURE 7. Endoscopic Healing and Improvement in Patients with CD Treated with EEN for 4 Weeks (N=28)

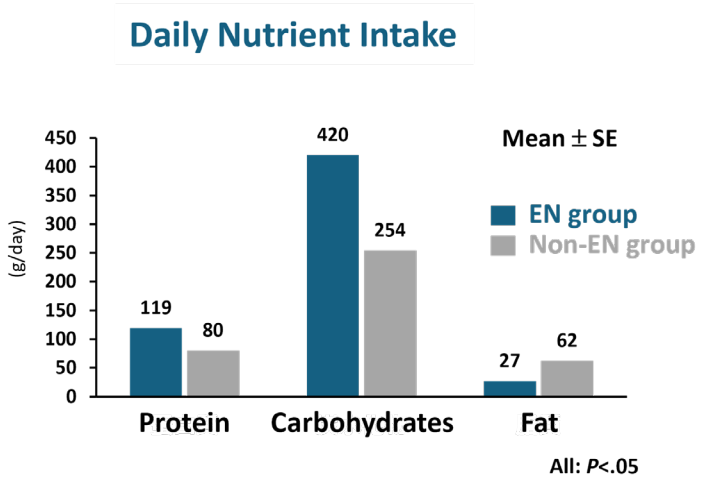


FIGURE 8. Impact of Half-ED Treatment on Daily Nutrient Intake in Patients with Quiescent CD at 12 Months (N=40)

Two meta-analysis were conducted to assess the role of EN in quiescent CD in Japan.[110,111] While results suggested EN is effective at maintaining remission in quiescent CD, the outcomes are not clear due to study limitations and no definite conclusions could be drawn. Only a few studies were available for assessment (5 to 7), sample sizes were small, and differences in control interventions did not allow for pooling of the data.

Another Cochrane meta-analysis compared the efficacy of EEN versus corticosteroids as induction therapy for active CD in pediatric and adult studies.[112] Twenty-seven studies were included in the analysis (N=1,011 subjects). The analysis concluded, with very low quality evidence, that EEN is significantly more effective in children with active CD than steroids, while steroids are significantly more effective in adults with active CD than EEN for induction therapy. Formula composition had no effect on results. These findings have influenced EN guidelines in Western countries.

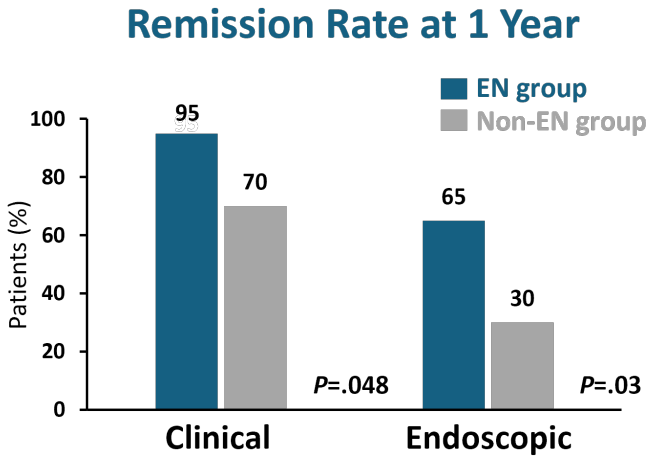


FIGURE 9. 1-year Remission Rates of a Half-ED Treatment Regimen After Surgical Resection for CD (N=40)

The Role of EN: Japan versus Western Countries

The role of EN differs in Japan and Western countries as delineated in **Table 5**. In Japan, EN is a first-line treatment along with medical therapy for both induction and maintenance of remission. Elemental formulas are preferred. This is contrasted with the role of EN in the West, where it is typically utilized to address nutritional or growth impairments. For the purposes of induction therapy, it is recommended as a first-line therapy in pediatrics, whereas it is used in adults when steroid therapy is not feasible. For maintenance, Western countries typically use EN when nutritional status cannot be maintained with diet alone. Western countries do not recommend elemental formula due to high cost and low palatability but otherwise do not differentiate between other formula types. The mode of administration does not differ between the Japanese and Western experience: Oral intake is preferred, and when not feasible, a nasogastric tube is used. Administration may also be done via a gastrostomy tube. Overall, EN is an established first-line therapy for induction and maintenance of remission in Japan but mainly utilized in the West for nutritional

support or when obstacles to pharmaceutical therapy are present.

TABLE 5. Role of EN in Japan versus Western Countries

	Japan	Western Countries
Indication for Induction	First-line treatment along with medical therapy in the absence of intestinal obstruction or complex fistulas	• Addressing nutritional or growth impairments • Pediatrics: First-line treatment • Adults: When steroid treatment is not feasible
Indication for Maintenance	First-line treatment along with drug therapy	When nutritional status cannot be maintained with diet alone
Formula Type	Elemental formulas are commonly used due to their amino acid-based nitrogen source and low-fat content	• No significant difference has been observed in efficacy among formula types • Elemental formulas are not recommended due to their high cost and poor palatability
Mode of Administration	• When oral intake is not possible or large volumes are required, nasogastric tube feeding is used • May also be administered via a gastrostomy tube	

EN Funding in Japan

All formula, including higher-cost elemental formula, are covered by tax revenue through the national or local government in Japan via a medical subsidy program. The program is for patients with designated diseases, such as UC and CD. The majority of IBD patients' medical expenses are funded through the subsidy and patients are left with a small out-of-pocket contribution.

Action Items

Utilize EN as Treatment

In Japan, EN is used as treatment while in the West, EN is often utilized to improve a patient's nutritional status. Use as a nutritional supplement has proven to be a barrier to insurance coverage in the US.

Conduct Larger Trials on EN

Larger clinical trials are needed to establish stronger evidence supporting the broader use of enteral formulas.

Create More Palatable, Cost-Effective Formulas to Improve Compliance

Creating more palatable and cost-effective formulas to improve patient adherence is crucial for achieving better treatment outcomes.

Appendix 3: Use of Nutritional Therapy in Guidelines of Treatment for Crohn's Disease

Despite the availability of many biologics and targeted agents for CD, many families prefer a treatment option that is not immunosuppressive. The MNT offers this opportunity. EN has classically been the only MNT available for CD, but recently whole-food diets designed to manage the disease have been showing efficacy.

Review of the Guidelines

The first joint ECCO/ESPGHAN guidelines for Crohn's disease were published in 2014 and made 2 recommendations regarding EN in pediatric patients with CD:[113]

1. EEN is recommended as first-line therapy to induce remission in children with active luminal CD.
2. Partial enteral nutrition (PEN) should not be used for induction of remission.

The 2014 treatment algorithm recommended 6 to 8 weeks of EEN in mild-to-moderate CD if well tolerated. If the patient had severe disease or failed to respond to EEN by 1 to 2 weeks, they would then move to prednisone for induction therapy.

When guidelines were updated in 2020, they included only 1 statement on EN use:

1. In children with active luminal CD, dietary therapy with EEN is recommended as first-line therapy for induction of remission.

Patients with severe growth delay or complications, such as extensive disease, deep ulcers, or stricturing disease without prestenotic dilation, then upfront therapy with an anti-TNF agent with or without an immunomodulator would additionally be considered.[22]

The 2020 ECCO guidelines for the treatment of CD in adults made no recommendations for nutritional therapy at all.[114] In 2024, the updated ECCO guidelines made a soft recommendation for the use of EN as induction therapy "in patients with mild-to-moderate CD who are motivated to adhere to dietary therapy, have access to dietetic support, and prefer to avoid corticosteroids [weak recommendation, very low-quality evidence.] [Consensus: 100%]."[115]

Evidence for MNT in CD

EEN

Historic studies and ongoing research have all indicated that EEN is efficacious in pediatric Crohn's disease. A 2022 meta-analysis of 46 studies ascertained the effects of EEN on clinical and laboratory indicators, as measured by the pediatric Crohn's disease activity index (PCDAI), inflammatory biomarkers, and biochemical parameters, when used for

induction.[116] Results demonstrated an improvement in PCDAI score, calprotectin, CRP, ESR, albumin, hemoglobin, and height when children with CD were treated with EEN. Another meta-analysis showed EEN was as effective as corticosteroids for induction therapy with no difference detected in relapse rate at 1 year.[117] Additionally, EEN was associated with a significantly higher likelihood of achieving endoscopic and histologic mucosal healing and a lower PCDAI score than corticosteroids.[117]

Adult studies have demonstrated variability in efficacy and the intervention is not often utilized in adults due to poor compliance and unpalatability. The studies conducted have also suffered from limitations that have made conclusions challenging, such as narrow delineation of baseline characteristics (disease location, disease duration, age at diagnosis) or differences in study populations.[118] The monotonous therapeutic strategy of EEN reinforces that it is only to be used as a short-term intervention for induction; there is no strategy after EEN for maintenance therapy.[119] Additionally, EEN reduces microbiome diversity, short chain fatty acid production, is devoid of fiber, and may aggravate or cause disordered eating. Due to the challenges in the sustainability of EEN, clinical practice in Europe is moving to replace it with whole-food diets developed specifically for the treatment of CD, such as the Crohn's Disease Exclusion Diet (CDED), Crohn's Disease Treatment with EATing (CD-TREAT), Specific Carbohydrate Diet (SCD), Mediterranean Diet, and Tasty and Healthy (T&H).

Crohn's Disease Exclusion Diet (CDED)

The CDED is a whole-food dietary intervention that is applied in a phasic approach and supplemented with partial enteral nutrition (PEN). The diet excludes foods known to affect the health of the patient and/or microbiota, incorporates foods known to promote rebiosis, and allows for a balanced diet to help encourage acceptability. The diet is combined with PEN, which is progressively tapered off by 12 weeks (**Table 1**).[1,12] Patients then enter a maintenance phase, but research has not yet validated the efficacy of CDED for maintenance.

A randomized controlled trial compared CDED + PEN versus EEN followed by PEN in children with mild-to-moderate CD.[12] The CDED treatment arm received CDED + 50% PEN for 6 weeks followed by CDED +25% PEN for another 6 weeks (**Figure 10**). The EEN treatment arm received EEN for 6 weeks followed by a free diet + 25% PEN for 6 weeks. Tolerability at 6 weeks (primary endpoint) was higher in the CDED arm (97.5% vs 73.6%, P=0.002). At Week 6, no statistically significant difference between secondary endpoints was detected (compliance, response, corticosteroid-free remission, remission PCDAI<10). Both interventions induced significant reductions from baseline disease activity, inflammatory markers, and fecal calprotectin by Week 6. When patients randomized to EEN entered Stage 2 of the intervention, a nonsignificant increase in fecal calprotectin was observed and a significant decline in sustained corticosteroid-free remission was noted with the gradual introduction of a free oral diet. However, those in the CDED+PEN group were more likely to sustain remission. By Week 12, patients randomized to the CDED

intervention had significantly greater corticosteroid-free remission, normal CRP remission, and sustained remission PCDAI≤10 than those initially randomized to EEN. There was also a continued downward trend in fecal calprotectin.

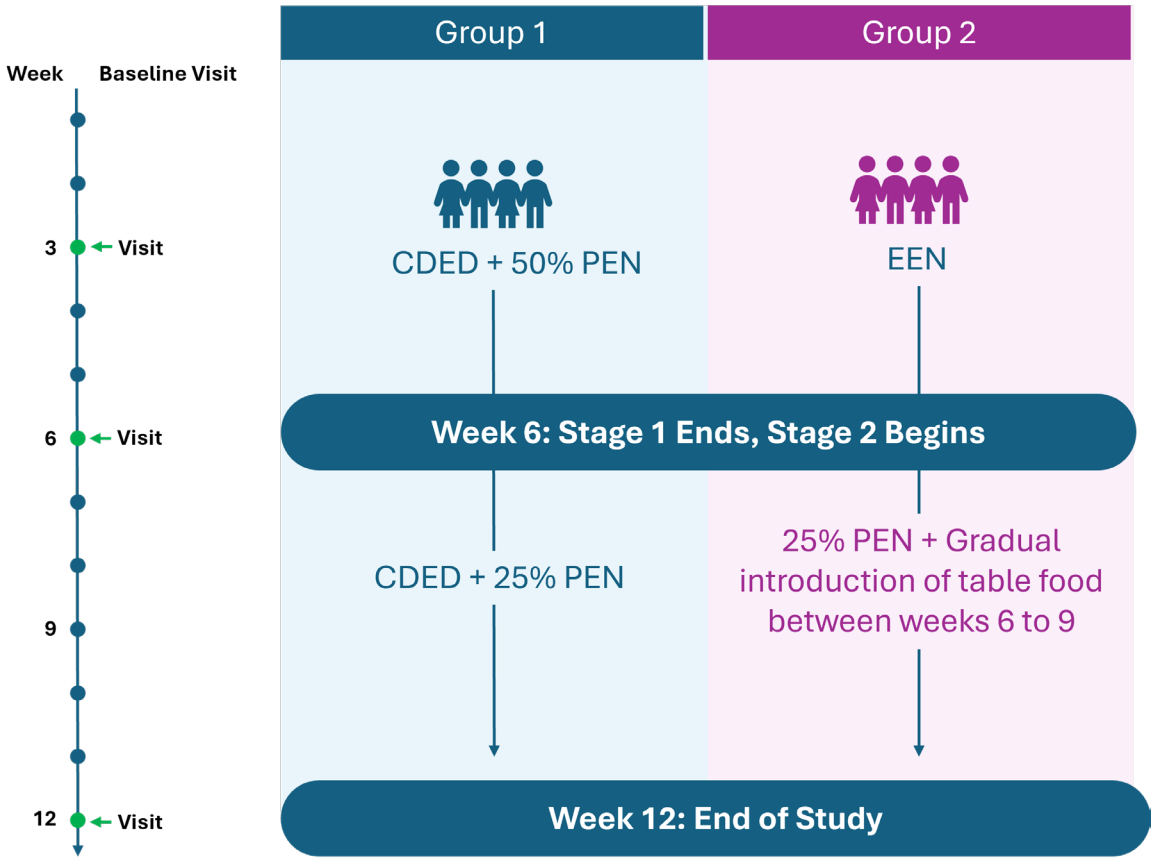


FIGURE 10. Study Schematic of a Clinical Trial Assessing CDED + PEN versus EEN Followed by PEN in Pediatric Mild-to-Moderate CD

Microbiota changes were also different between the 2 study arms. There was an overall decrease from baseline *Haemophilus, Veillonella, Bifidobacterium, Prevotella,* and *Anaerostipes* concentrations; and an overall increase from baseline *Oscillibacter* and *Roseburia* concentrations. The changes in taxa were similar between the 2 study groups. Those randomized to CDED + PEN additionally saw decreases in *Lachnospira* and increases in *Subdoligranulum, Blautia, Ruminococcus,* and *Erysipelotrichaceae*. CDED + PEN subjects continued to experience microbiota changes throughout the study period, including Stage 2 (Weeks 6 to 12). However, EEN subjects generally saw a rebound to pretreatment microbiota levels in Stage 2.[12]

Clinical studies have demonstrated a rapid response with CDED + PEN.[120] A response at 3 weeks on either EEN or CDED + PEN is a high predictor of remission at 6 weeks. Because of its higher tolerability and palatability and similar efficacy, CDED has become the standard of care for pediatric CD in many European institutions. However, some individuals may

prefer EEN due to its extreme simplicity. For EEN, patients can use any formula. For CDED + PEN, patients do not need to use the same formula throughout the entire treatment period; they should consume enough formula to reach their target caloric intake.

Data in adults suggest CDED alone or with PEN is an effective induction and maintenance strategy for those with mild-to-moderate disease, potentially leading to endoscopic remission.[121] An open-label study randomly assigned 44 adults to CDED + PEN (N=20) or CDED alone (N=24) to assess the impact of the intervention on clinical remission rates at Week 6. The study achieved remission rates of 68% for CDED +PEN and 57% CDED alone; no statistically significant differences were observed between groups. At Week 24, 35% of the study cohort achieved endoscopic remission, including 6 subjects who were on CDED alone. This intervention may not be appropriate for pediatrics as children are rarely seen with very mild disease, but it is a sustainable long-term option for adults, with another study suggesting efficacy in multiple CD phenotypes and presentations.[122]

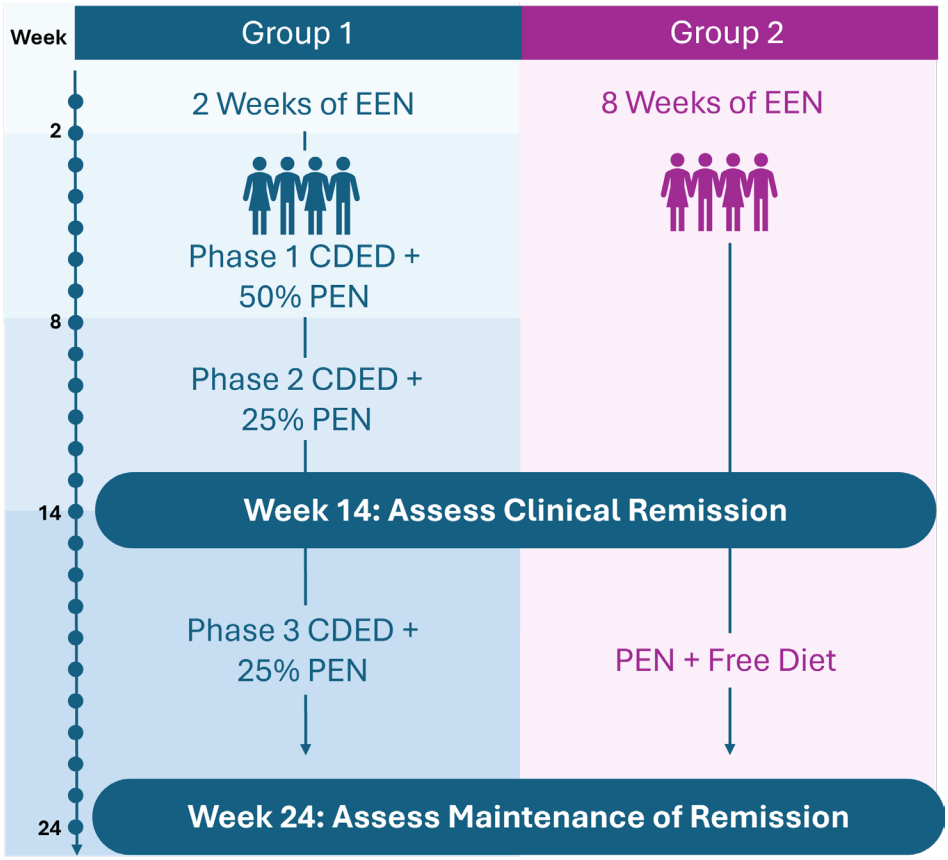


FIGURE 11. Study Schematic of a Clinical Trial Assessing the Comparative Efficacy of EEN Followed by CDED + PEN versus EEN Followed by PEN + Free Diet in Mild-to-Severe CD

The impact of a modified CDED diet on clinical remission rates was also investigated.[123] Participants with mild-to-severe CD were randomized into 2 groups (**Figure 11**). Group 1 received 2 weeks of EEN followed by CDED + PEN. Group 2 received 8 weeks of EEN

followed by PEN + free diet. Clinical remission rates were assessed at Week 14 and maintenance of remission was assessed at Week 24. The enrollment target was not met due to COVID-19 restrictions. No significant difference was observed between the 2 groups at Week 14: 70% of Group 1 and 61.5% of Group 2 achieved sustained corticosteroid free remission. However, body mass index (BMI) significantly improved in the CDED group compared to EEN. While the study was underpowered, the modified CDED strategy (EEN followed by CDED + PEN) was effective in inducing remission and sustaining it up to 24 weeks.

Crohn's Disease Treatment with EATing (CD-TREAT)

The CD-TREAT diet is a whole-foods replica of EEN. The diet replicates the nutritional composition of EEN and its effect on the microbiome but with ordinary food instead of formula. The diet avoids lactose and gluten. A clinical study of 28 healthy volunteers tested the effect of CD-TREAT on the gut microbiome. The study was augmented by experimentation in CD rat models to observe the effect of the diet on anti-inflammatory markers and microbiome composition. It was then followed by testing in 5 children with active CD to observe its efficacy in inducing clinical remission and normalizing laboratory markers of inflammation.[124] Healthy volunteers were randomized to EEN or CD-TREAT for 7 days each with a 2-week washout period in between each intervention; rats were randomized to CD-TREAT, EEN, or regular chow; and children were given a 4-week CD-TREAT diet with food delivery services. Children could continue the diet for up to an additional two 4-week cycles if they continued to demonstrate response/remission. Non-responding children exited the trial.

Results from healthy volunteers demonstrated that both interventions caused a significant reduction in the concentration of total fecal bacteria, shifted the β-diversity index in the same direction, and changed the metabolome in the same direction. Rat studies were largely confirmatory. Results from the pediatric patients with CD demonstrated a significant reduction from baseline wPCDAI over 8 weeks, with 4 children responding to treatment and 3 entering clinical remission. Children also saw a reduction from baseline fecal calprotectin at Week 4 and Week 8.[124]

Specific Carbohydrate Diet (SCD) and Mediterranean Diet (MD) for CD

The DINE trial compared the efficacy of the specific carbohydrate diet (SCD) versus the Mediterranean diet (MD) on mild-to-moderate adult patients with CD (N=191).[125] Results indicated no difference between the diets when comparing rates of symptomatic remission, CRP, and fecal calprotectin response by Week 6 (**Figure 12**). Considering the poor CRP response and the availability of more efficacious diets, the SCD and the MD likely do not have a role to play in induction.

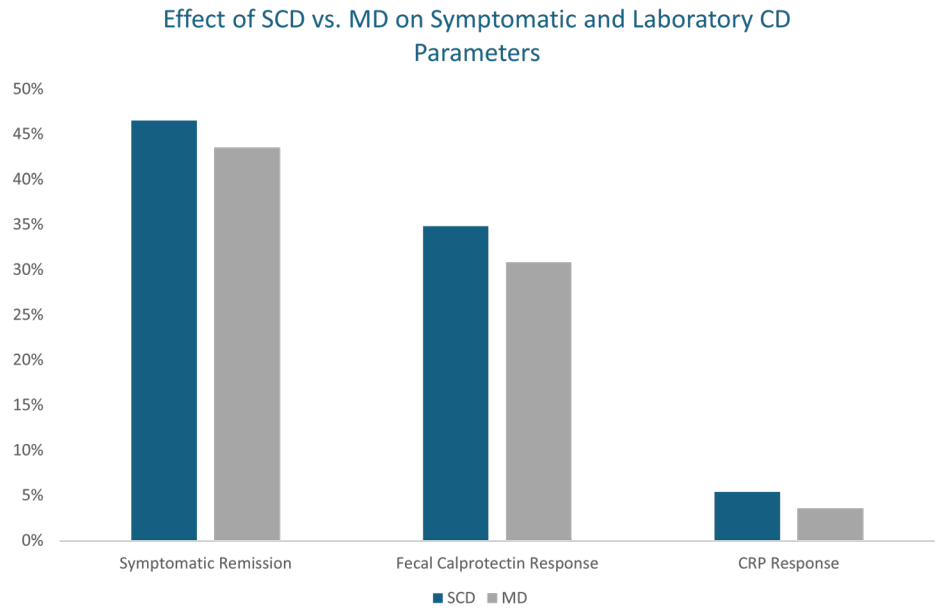


FIGURE 12. Effect of SCD versus MD on Symptomatic Remission, Fecal Calprotectin Response, and CRP Response

Tasty and Healthy (T&H)

The Tasty and Healthy (T&H) diet is a whole foods, formula-free diet developed in Jerusalem. The diet excludes processed food, gluten, red meat, and diary (except plain yogurt), and unlike CDED, has no mandatory ingredients or formula requirements. A recent randomized controlled trial compared T&H to EEN in patients aged from 6 to 25 with mild-to-moderate CD or 8 weeks (N=83).[126] Improvements from baseline were observed with both interventions, however no group differences were seen in remission rates, mucosal healing, fecal calprotectin levels, CRP, and ESR in the intent-to-treat population. The T&H diet had significantly greater tolerability than EEN (88% vs 52%, *P*<0.001), making the formula-free diet a flexible and tolerable alternative to EEN with comparable efficacy.

Commentary: What is the Goal?

What is the goal of dietary therapy in CD? According to ECCO/ESPGHAN 2020 guidelines, if a patient responds to EEN or steroids, they will then move to immunomodulators.[22] However, data have shown early azathioprine use in newly diagnosed adults with CD is no different from placebo and controversy has developed over the role of thiopurines in CD.[127,128] Methotrexate has a lot of issues with toxicity and its role is uncertain when safer agents are now available. If thiopurines and methotrexate are not going to be used and patients will go straight to highly effective treatment with anti-TNF agents, what then is the purpose of subjecting them to a difficult nutritional intervention upfront?

There is no single strategy that will fit all patients with CD. In the world of modern highly effective medical therapies, there is no need for a full course of EEN. While EEN will

continue to play a role in IBD (eg, in the perioperative setting), there is no need for a full course of EEN as induction therapy in the modern world of precision medicine. When we explore EEN and dietary interventions alongside modern medication, options for a variety of treatment combinations emerge (**Figure 13**). While this adds flexibility, it also makes it very difficult to study nutritional interventions.

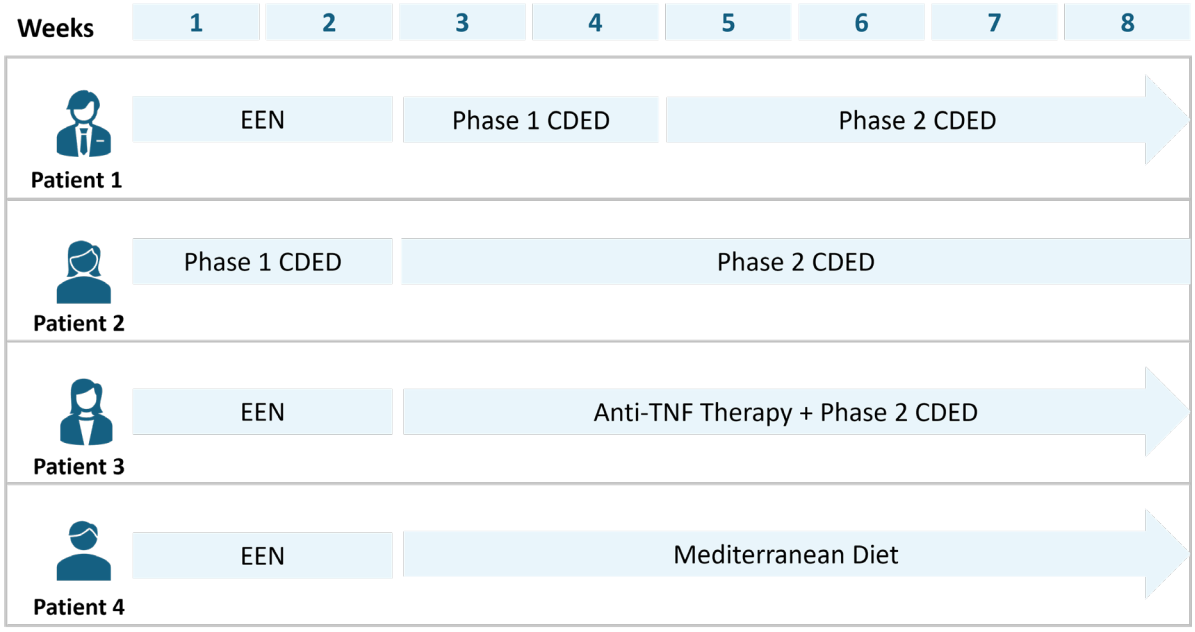


FIGURE 13. Sample Dietary Intervention Plans. Dietary Interventions can be used in a Variety of Combinations and With Advanced Medical Therapies, such as Biologics

Combination Therapy

Combining nutritional interventions with biologics has been investigated as a method to improve upon the efficacy, lessen loss of response, and improve treatment tolerance among patients with CD. Data from a real-world study in China from 197 patients with ileal or ileocolonic mild-to-moderate CD demonstrated that treatment with a biologic in combination with EEN resulted in higher rates of clinical response (95% vs 66%), clinical remission (87% vs 52.6%), and endoscopic response (91.4% vs 47.4%), including mucosal healing (85.7% vs 23.7%) than those treated with a biologic alone at Week 16.[129] The advantage of the combination regimen over biologic alone was sustained throughout maintenance. Similar findings were observed with vedolizumab + EEN.[130] Once in remission, PEN has been shown to prevent clinical relapse based on findings from a meta-analysis with a 0.5 to 2-year follow-up period. [131]

Looking Ahead: 2026 Guidelines

The 2026 guidelines are currently in progress, but major changes are expected. The categorization of disease as mild, moderate, or severe may likely be replaced with

categories based on complication and risk. Nutritional therapy will likely be positioned first-line as a bridge drug therapy, either with anti-TNFs or immunomodulators depending upon a patient's risk. CDED + PEN will likely be positioned as an alternative to EEN based on the data. While CD-TREAT and T&H have shown promising preliminary results, more data is needed.

More research and guidance are needed on how nutritional therapy should be sequenced alongside newly approved biologics, older biologics, and targeted small molecules. Considering the chronic nature of CD, more research is required on the use of adjunctive dietary strategies during maintenance-phase treatment with pharmaceuticals.

Action Items

Research How MNT Can Optimize Biologics

1. Secure funding for research and conduct research on how medical nutrition can optimize the efficacy, safety, and longevity of biologics in a "combination therapy" approach.
2. Encourage drug development that includes the use of MNT.

Next Steps

Data on MNT in IBD, particularly as induction therapy in pediatric CD is compelling, but patients continue to lack access to this treatment option, which has been demonstrated to be safer and just as efficacious as corticosteroids. To carve a path forward for improved patient access to this nutrition-based treatment regimen, a payor and a legislative strategy need to be developed and enacted. This is largely disadvantaged by the lack of economic cost analyses demonstrating long-term cost effectiveness. While it is vital to collect prospective real-world data and incorporate cost analyses in all future clinical research as feasible, a health economist should be engaged in the interim to extrapolate existing data from research papers and registries to assess the cost-effectiveness of nutritional therapies.

In tandem with the development and collection of economic data, a legislative and payor plan needs to be developed and enacted. Focused legislative efforts will be more impactful than broad, sweeping efforts. This can be achieved by targeting key legislators and narrowing the scope of legislation to the population in whom data is most compelling—pediatric CD. Gaining approval in CD will allow for MNT utilization and expedite the generation of real-world data, facilitating future legislative expansion into the remaining affected disease states. Furthermore, a state-by-state mapping of the individuals affected by MNT inaccessibility needs to be created. This will allow for the identification of representatives and senators whose constituents are affected by legislation, as well as local stakeholders and advocates who can further apply pressure on their elected officials.

Concurrently, a payor strategy can be implemented in tandem with the legislative strategy once an economic analysis is available. This includes engaging current insurers, presenting cost-effectiveness data, and educating payors on the financial benefits of coverage, the use of MNT as *treatment* instead of nutritional supplementation, and the role and impact of MNT as combination therapy with current biologics.

The FDA and federal government have seen considerable reorganization in recent months, with an enhanced focus on nutrition and food as medicine. This has created a highly conducive environment for the reintroduction of past failed federal legislative efforts. Additionally, there are avenues for the incorporation of patients in the FDA decision-making process that have not been utilized by the nutrition industry. These include open public hearings at FDA Advisory Committee Meetings and FDA Patient Listening Sessions. The FDA has a successful patient-focused drug development program that can serve as a paradigm for a similar model in the nutrition center.

The FDA and third-party payors understand the language of combination therapy very well, but this path has not been pursued with MNT, despite some preliminary data on the benefits of MNT when used in combination with biologics. MNT stakeholders need

to engage the pharmaceutical manufacturers of biologics to research the impact of combination therapy and leverage the high-quality research expertise and funding they may provide as partners. This approach will allow stakeholders to engage CBER at the FDA, and per regulatory procedure, CBER will then have to engage patients in the decision-making process.

Finally, advocacy and education are vital to achieving coverage. Because patients cannot access MNT, providers do not use it and many do not know the benefits of MNT in IBD. Multidisciplinary provider education is necessary to advance data-driven utilization of MNT in accordance with guideline recommendations. Education on how to position MNT is also needed. MNT needs to be spotlighted at major medical meetings, congresses, and smaller local grand rounds in the same manner pharmaceutical interventions are discussed. The importance of working with a dietician and engaging them in care needs to be highlighted. Nutritional interventions for IBD will fail without the involvement of a dietician.

Detailed Action Items

Develop an Economic Cost Analysis

- Conduct a comparative effectiveness analysis in children that compares nutritional therapy to other options in inducing/maintaining remission
- Incorporate a systematic review and meta-analysis in any comparative effectiveness study
- Research should include costs and outcomes analysis using QALYS, comparing the treatments used in the comparative effectiveness analysis
- Publish and share results with stakeholders, including insurers, the FDA, industry, and Congress

Understand the Legislative Path and Narrow its Scope

Align coalition members to narrow the scope of the bill to pediatrics

- Introduce revised legislation at state and federal level
- Add adult coverage subsequently as additional evidence for use in adults is generated

Develop state-by-state mapping of who legislation is impacting

- Quantify the number of constituents impacted by IBD in each state
- Quantify the number of people who will be impacted by medical nutrition
- Develop coalition partnerships at the federal and state levels from the start

Carve Out New Opportunities for Working with the FDA

- Standardize the medical nutrition lexicon
- Modernize the interpretation of the Orphan Drug Act rather than create a new category for medical nutrition within the FDA
- Take advantage of the current administration's "Food is Medicine" approach to continue legislative efforts despite past failures
- Educate members at the Office of Critical Foods at the FDA
- Engage CDER and CBER if a "combination therapy" strategy between drugs/biologics and medical nutrition is pursued

Create a Payor Strategy

Once economic analysis is available, engage insurers around all forms of medical nutrition therapy

- Speak with current (not former) insurers and educate on the issue
- Include smaller regional plans and self-insured employers in education and discussion efforts; they may be more open to feedback and cost data
- Attempt to advance coverage where there is interest
- Explore partnerships with insurers' charitable foundations to advance combination research
- Utilize existing nutritional categories in place by the FDA, ensure medical nutrition therapy for IBD is included and begin leveraging these categories to engage payors
- Support a multidisciplinary approach to medical nutrition and the incorporation of dieticians/nutritionists as part of the clinical care team

Engage Pharmaceutical Stakeholders

- Secure funding for research and conduct research on how medical nutrition can optimize the efficacy, safety, and longevity of biologics in a "combination therapy" approach
- Encourage drug development that includes the use of medical nutrition therapy
- Add the patients' voice to the research, drug development, and approval process as it relates to incorporating medical nutrition therapy into IBD treatment regimens

Generate Real-World Evidence Supporting the Use of Medical Nutrition Therapy

- Create a path where real-world evidence and cost saving are part of the development process
- Generate data on the use of medical nutrition as *treatment* and its role in reducing side effects
- Educate healthcare professionals and patients on medical nutrition in IBD, including gaps in care and barriers to access

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