# An Innovative Medical Food Reduces Gastrointestinal Symptoms and Beneficially Alters Gut Microbiota in Adults with IBS and IBD

## A Multi-Clinic, Open-Label Study

**BACKGROUND**

The most common gastrointestinal (GI) disorder, irritable bowel syndrome (IBS), affects approximately 11% of the global population.[1] Less prevalent, inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis (UC), affects 1 to 1.3 million people in the U.S. and celiac disease affects about 1% of the general U.S. population.[2–4]

Compromised gut function, mucosal inflammation, and dysbiosis (alteration of the intestinal microbiota) contribute to the pathogenesis of IBS, IBD, and celiac disease.[5–10] Due to the high prevalence of nutrient deficiencies in individuals with IBD and celiac disease (as a result of nutrient malabsorption and malnutrition), nutritional support is recommended in addition to current clinical management plans.[11–13]

This Innovative Medical Food is formulated to provide nutritional support in the management of compromised gut function associated with digestive disorders and malabsorption. These symptoms may be associated with IBS, IBD, and celiac disease. This medical food provides a unique blend of macronutrients, micronutrients, and exclusive prebiotics selected for their ability to improve gut function, nutrient absorption, and intestinal microbiota.

**OBJECTIVE**

The primary objective of this study was to observe the effect of the Innovative Medical Food on GI symptoms and quality of life in adults with previously diagnosed IBS, IBD, and celiac disease. Exploratory aims were to determine the effect of Innovative Medical Food on a comprehensive stool analysis panel.

**METHODS**

This was an open-label study conducted under the guidance of the Functional Medicine Research Center® (Gig Harbor, WA), the clinical research arm of Metagenics, Inc. Participants were recruited from 4 U.S. clinic sites of medical, osteopathic, and naturopathic doctors. Adults aged 21 to 75 y/o with a previous diagnosis of IBS, UC, Crohn's disease, or celiac disease were eligible to join the study. Participants were instructed to consume 1 serving (2 scoops) of the Innovative Medical Food twice daily for 6 weeks.

At baseline and study end, participants completed the Gastrointestinal Quality of Life Index (GIQLI), a validated 36-item questionnaire that was designed for patients with disorders of the esophagus, stomach, gallbladder, pancreas, small intestine, colon, and rectum.[14] The GIQLI yields a total score and 4 subdomain scores, and can detect change over time; higher scores are consistent with a better quality of life.

In addition, participants were asked to complete condition-specific questionnaires: the Digestive Symptom Frequency Questionnaire (DSFQ) if they had IBS, or the Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ) if they had IBD.[15–18]

Stool samples were collected at baseline and study end. They were analyzed using the Genova GI Effects® Comprehensive Stool Profile to assess gut microbiota short-chain fatty acid (SCFA) levels and biomarkers that indicate digestive and absorptive function, gut inflammation, and immunology.[19]

Most data are expressed as mean±SD. Changes from baseline to 6 weeks were analyzed using 2-sided paired t-tests. Gut microbiota PCR data were log-transformed prior to analysis. A value of $p<0.05$ was considered statistically significant.

**RESULTS**

**Participant Characteristics**

Twelve individuals completed the study. Three additional participants began the study, but dropped out citing GI upset, worsening of pre-existing GI symptoms, and an acute illness unrelated to the study intervention.

The individuals that completed the study were 7 men and 5 women ranging in age from 22-60 (mean 31.4±10.5 y/o) with a mean weight of 162.8±33.1 lb. and a mean BMI of 23.8±3.4 kg/m$^2$. They identified racially as White (8), White/Native American (2), Black (1), or Hispanic/Latino (1). The pre-existing conditions that made them eligible for the study were IBS (7), UC (4), and celiac disease (1).

**GI Symptoms and Quality of Life (GIQLI) Scores Improved**

All participants, regardless of their pre-existing condition, were asked to complete the GIQLI. Overall, total scores improved by

a mean of 20.8% (p=0.020) from baseline to the end of the study (**Table 1**). Scores for the GI symptoms domain and the social function domain also improved significantly.

**Table 1**. GIQLI scores at baseline and 6 weeks among participants who completed the study

| | Scores | Mean % change | P value | Score range |
|---|---|---|---|---|
| **Total score** | Baseline: 94.3±25.5<br>6 weeks: 109.4±19.2 | 20.8% | **0.020** | 0-144 |
| **Subdomain** | | | | |
| **GI symptoms** | Baseline: 53.3±10.3<br>6 weeks: 61.4±7.7 | 18.1% | **0.022** | 0-76 |
| **Social function** | Baseline: 10.7±3.8<br>6 weeks: 12.3±3.7 | 18.4% | **0.004** | 0-16 |
| **Emotional function** | Baseline: 12.0±5.8<br>6 weeks: 14.7± 4.5 | 46.5% | 0.139 | 0-20 |
| **Physical function** | Baseline: 15.6±7.4<br>6 weeks: 17.8±6.1 | 36.5% | 0.164 | 0-28 |

**IBDQ Scores Showed a Trend Toward Improvement**

The 4 participants with UC also completed the IBDQ, which yields a total score and 4 subdomain scores. The total score improved by a mean of 43.6% (p=0.078), and the systemic symptoms subdomain score improvement of 66.9% was statistically significant (p=0.0002). The 7 participants with IBS also completed the DSFQ and indicated a minor improvement in mean score by 10.3% (p=0.522).

**Enhanced Production of SCFAs, Including Butyrate**

Total SCFA levels include the sum of butyrate, acetate, and propionate. After 6 weeks, butyrate levels increased by a mean of 72.7% (p=0.022; **Figure 1**) and total SCFA levels increased by a mean of 72.2% (p=0.026; **Figure 1**).

*Roseburia spp.* and *Faecalibacterium prausnitzii* are butyrate-producing microbiota.[20] The GI Effects® Comprehensive Stool Profile identifies commensal (normally present) bacteria via PCR. In this study, *Roseburia* spp. and *Faecalibacterium prausnitzii* levels increased 7-fold (p=0.063) and 18-fold (p=0.032) on average, respectively (p values were calculated using paired t-tests of the log transformed data).

**Resolution of Potentially Harmful Microorganisms**

In addition to identifying commensal bacteria, the GI Effects® Comprehensive Stool Profile also identifies bacteria and yeast using traditional culture methods and mass spectrometry. The identified species may be classified as potentially harmful bacteria. Out of the 12 participants that completed the study, a total of 8 potentially harmful bacteria species were identified at baseline. At the end of the study, 7 of the 8 total potentially harmful bacteria species were no longer detected. In contrast, only 2 potentially harmful strains (not identified at baseline) were present at the end of the study.

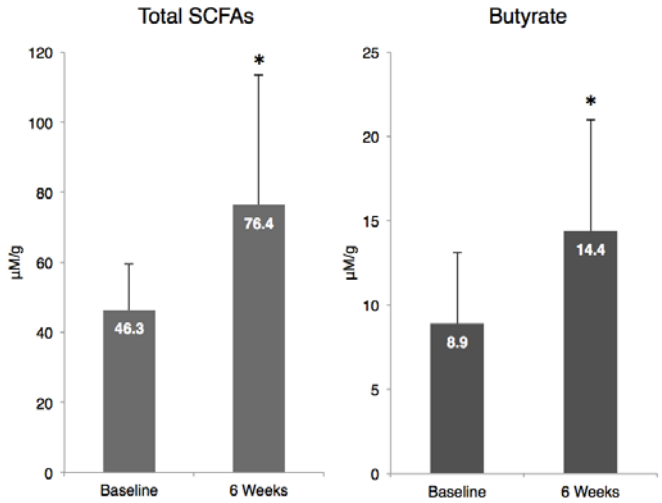


**Figure 1**. Levels of total SCFAs and butyrate at baseline and 6 weeks among participants who completed the study. Error bars indicate standard deviation. *p<0.05.

**Increased Levels of *Bifidobacterium***

After 6 weeks, levels of *Bifidobacterium* spp. increased on average by 19-fold (p=0.026 via a paired t-test of the log transformed data; **Figure 2**).

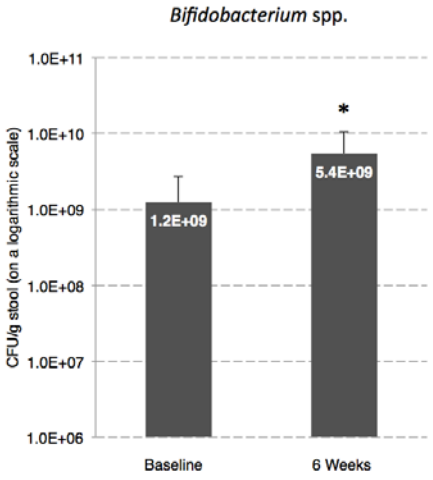


**Figure 2**. Levels of *Bifidobacterium* spp. at baseline and 6 weeks. Paired t-test was conducted on log-transformed data. *p<0.05.

## DISCUSSION

### Proposed Mechanisms of Innovative Medical Food Ingredients

Altering the composition of the intestinal microbiota using prebiotics holds promise as a therapeutic strategy for addressing compromised gut function associated with these GI conditions.[9,21,22] This Innovative Medical Food contains a proprietary blend of prebiotics: a nature identical 2'-fucosyllactose (2'-FL) and isomalto-oligosaccharides (IMOs). Prebiotics are non-digestible food and plant ingredients, mostly small carbohydrate polymers known as oligosaccharides, which beneficially affect the host through their selective metabolism in the intestinal tract.[23]

2'-FL is a prebiotic found in human breast milk. Several functions have been attributed to 2'-FL, including the ability to support the growth of beneficial microbiota (including *Bifidobacterium*), inducing the production of SCFAs (an energy substrate for colonic epithelial cells), and regulating gut motility (by reducing the frequency and velocity of contractions).[24–29]

2'-FL also supports GI health by blocking certain potentially harmful bacterial strains from adhering to their host cell receptors; 2'-FL mimics host cell surface receptors and acts as a decoy.[27] 2'-FL has been shown to act as an anti-adhesive antimicrobial to *Campylobacter jejuni*, *Vibrio cholera, Escherichia coli,* and Norovirus.[27,30,31]

IMOs are a well-tolerated prebiotic soluble fiber. Short chain oligosaccharides, like IMOs, support the production of SCFAs as end products of GI fermentation. These molecules decrease intra-luminal pH, directly inhibit the growth and activities of harmful microorganisms, and encourage the growth of *Bifidobacterium*, which compete with potentially harmful microorganisms for nutrients and epithelial adhesion sites.[32–35]

Patients with IBS and IBD have lower levels of butyrate-producing microorganisms.[36,37] For example, *Roseburia hominis* and *Faecalibacterium prausnitzii* are butyrate-producing species known to be deficient in patients with IBD; both species display an inverse correlation with UC disease activity.[38] Butyrate-producing bacteria improve intestinal barrier function and reduce methane-producing microorganisms in the human colon, which may reduce abdominal gas.[36] Previous research has shown that exogenous butyrate shows promise as a novel therapy for IBS and IBD.[39,40]

It is plausible that the mechanism for increased production of SCFAs including butyrate, increased levels of *Bifidobacterium*, and reduction of potentially harmful microorganisms in the study subjects may be related to the Innovative Medical Food key ingredients, such as 2'-FL and IMOs. These changes may have contributed to the reduction in GI symptoms demonstrated in this study.

## SUMMARY

This open-label, multi-clinic study in 12 patients with digestive disorders demonstrated that consuming 2 servings daily of the Innovative Medical Food for 6 weeks:

- Reduced GI symptoms and improved overall GI quality of life
- Increased production of SCFAs, including butyrate
- Increased levels of *Bifidobacterium* spp.
- Reduced potential harmful intestinal microbiota

Despite the limited sample size in this preliminary study, the Innovative Medical Food offers promise as a novel nutritional therapy for patients with compromised gut function. Further research is recommended to confirm these results in a larger patient population under controlled conditions.

**REFERENCES**


1. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(7):712-721.
2. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol*. 2007;5(12):1424-1429.
3. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology*. 2004;126(6):1504-1517.
4. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. *Am J Gastroenterol*. 2012;107:1538-1544; quiz 1537, 1545.
5. Wald A. Pathophysiology of irritable bowel syndrome. *Up To Date*. 2014. Available at: http://www.uptodate.com/contents/pathophysiology-of-irritable-bowel-syndrome
6. Peppercorn MA, Cheifetz AS. Definition, epidemiology, and risk factors in inflammatory bowel disease. *Up To Date*. 2015. Available at: http://www.uptodate.com/contents/definition-epidemiology-and-risk-factors-in-inflammatory-bowel-disease
7. Guandalini S, Assiri A. Celiac disease: a review. *JAMA Pediatr*. 2014;168:272-278.
8. González-Castro AM, Martínez C, Salvo-Romero E, et al. Mucosal pathobiology and molecular signature of epithelial barrier dysfunction in the small intestine in irritable bowel syndrome. *J Gastroenterol Hepatol*. 2016.
9. Orel R, Kamhi Trop T. Intestinal microbiota, probiotics and prebiotics in inflammatory bowel disease. *World J Gastroenterol*. 2014;20(33):11505-11524.
10. Di Cagno R, De Angelis M, De Pasquale I, et al. Duodenal and faecal microbiota of celiac children: molecular, phenotype and metabolome characterization. *BMC Microbiol*. 2011;11(1):219.
11. Massironi S, Rossi RE, Cavalcoli FA, Valle S Della, Fraquelli M, Conte D. Nutritional deficiencies in inflammatory bowel disease: therapeutic approaches. *Clin Nutr*. 2013;32(6):904-910.
12. DeLegge MH. Nutrition and dietary interventions in adults with inflammatory bowel disease. *Up To Date*. 2015. Available at: http://www.uptodate.com/contents/nutrition-and-dietary-interventions-in-adults-with-inflammatory-bowel-disease
13. Ciclitira PJ. Management of Celiac Disease in Adults. *Up To Date*. 2015. Available at: http://www.uptodate.com/contents/management-of-celiac-disease-in-adults
14. Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg*. 1995;82(2):216-222.
15. Azpiroz F, Guyonnet D, Donazzolo Y, Gendre D, Tanguy J, Guarner F. Digestive symptoms in healthy people and subjects with irritable bowel syndrome. *J Clin Gastroenterol*. 2015;49(7):e64-e70.
16. Guyonnet D, Schlumberger A, Mhamdi L, Jakob S, Chassany O. Fermented milk containing *Bifidobacterium lactis* DN-173 010 improves gastrointestinal well-being and digestive symptoms in women reporting minor digestive symptoms: a randomised, double-blind, parallel, controlled study. *Br J Nutr*. 2009;102(11):1654-1662.
17. Guyatt G, Mitchell A, Irvine JE, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology*. 1989;96:804-810.
18. Häuser W, Gold J, Stallmach A, Caspary WF, Stein J. Development and validation of the Celiac Disease Questionnaire (CDQ), a disease-specific health-related quality of life measure for adult patients with celiac disease. *J Clin Gastroenterol*. 2007;41(2):157-166.
19. GI Effects® Comprehensive Profile - Stool. Available at: https://www.gdx.net/product/gi-effects-comprehensive-stool-test.
20. Pryde SE, Duncan SH, Hold GL, Stewart CS, Flint HJ. The microbiology of butyrate formation in the human colon. *FEMS Microbiol Lett*. 2002;217(2):133-139.
21. Leenen CHM, Dieleman LA. Inulin and oligofructose in chronic inflammatory bowel disease. *J Nutr*. 2007;137(11 Suppl):2572S-2575S.
22. Marasco G, Di Biase AR, Schiumerini R, et al. Gut microbiota and celiac Disease. *Dig Dis Sci*. 2016;61(6):1-12.
23. Gibson GR, Probert HM, Loo J Van, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutr Res Rev*. 2004;17(2):259-275.
24. Yu ZT, Chen C, Kling DE, et al. The principal fucosylated oligosaccharides of human milk exhibit prebiotic properties on cultured infant microbiota. *Glycobiology*. 2013;23(2):169-177.
25. Vester Boler BM, Rossoni Serao MC, Faber TA, et al. In vitro fermentation characteristics of select nondigestible oligosaccharides by infant fecal inocula. *J Agric Food Chem*. 2013;61(9):2109-2119.
26. Bode L, Jantscher-krenn E. Structure-Function Relationships of Human Milk Oligosaccharides. *Adv Nutr An Int Rev J*. 2012;3(3):383-391.
27. Castanys-Muñoz E, Martin MJ, Prieto PA. 2'-fucosyllactose: An abundant, genetically determined soluble glycan present in human milk. *Nutr Rev*. 2013;71(12):773-789.
28. Morrow AL, Ruiz-Palacios GM, Altaye M, et al. Human milk oligosaccharides are associated with protection against diarrhea in breast-fed infants. *J Pediatr*. 2004;145(3):297-303.
29. Ruiz-Palacios GM, Cervantes LE, Ramos P, Chavez-Munguia B, Newburg DS. Campylobacter jejuni binds intestinal H(O) antigen (Fuc alpha 1, 2Gal beta 1, 4GlcNAc), and fucosyloligosaccharides of human milk inhibit its binding and infection. *J Biol Chem*. 2003;278(16):14112-14120.
30. El-Hawiet A, Kitova EN, Klassen JS. Recognition of human milk oligosaccharides by bacterial exotoxins. *Glycobiology*. 2015;25(8):845-854.
31. Weichert S, Koromyslova A, Singh BK, et al. Structural basis for norovirus inhibition by human milk oligosaccharides. *J Virol*. 2016;90(9):4843-4848.
32. Yen CH, Tseng YH, Kuo YW, Lee MC, Chen HL. Long-term supplementation of isomalto-oligosaccharides improved colonic microflora profile, bowel function, and blood cholesterol levels in constipated elderly people-A placebo-controlled, diet-controlled trial. *Nutrition*. 2011;27(4):445-450.
33. Koleva P, Ketabi A, Valcheva R, Gänzle MG, Dieleman LA. Chemically defined diet alters the protective properties of fructo-oligosaccharides and isomalto-oligosaccharides in HLA-B27 transgenic rats. *PLoS One*. 2014;9(11):e111717.
34. Hu Y, Ketabi A, Buchko A, Gänzle MG. Metabolism of isomalto-oligosaccharides by *Lactobacillus reuteri* and bifidobacteria. *Lett Appl Microbiol*. 2013;57(2):108-114.
35. Goffin D, Delzenne N, Blecker C, Hanon E, Deroanne C, Paquot M. Will isomalto-oligosaccharides, a well-established functional food in Asia, break through the European and American market? The status of knowledge on these prebiotics. *Crit Rev Food Sci Nutr*. 2011;51(5):394-409.
36. Pozuelo M, Panda S, Santiago a, et al. Reduction of butyrate- and methane-producing microorganisms in patients with irritable bowel syndrome. *Sci Rep*. 2015;5:12693.
37. Takahashi K, Nishida A, Fujimoto T, et al. Reduced abundance of butyrate-producing bacteria species in the fecal microbial community in Crohn's disease. *Digestion*. 2016;93(1):59-65.
38. Machiels K, Joossens M, Sabino J, et al. A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut*. 2013:1-9.
39. Załęski A, Banaszkiewicz A, Walkowiak J. Butyric acid in irritable bowel syndrome. *Prz Gastroenterol*. 2013;8(6):350-353.
40. Breuer RI, Soergel KH, Lashner BA, et al. Short chain fatty acid rectal irrigation for left-sided ulcerative colitis: a randomised, placebo controlled trial. *Gut*. 1997;40(4):485-491.