MEDICAL MUTUAL®

Fecal Analysis in the Diagnosis of Intestinal Dysbiosis and Fecal Microbiota Transplant Testing

Policy Number: AHS – G2060 – Fecal Analysis in the Diagnosis of Intestinal Dysbiosis and Fecal Microbiota Transplant Testing	Prior Policy Name and Number, as applicable: • AHS – G2060 – Fecal Analysis in the Diagnosis of Intestinal Dysbiosis
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I. Policy Description

Intestinal dysbiosis is defined as a disruption or imbalance of the intestinal microbial ecology (Guinane & Cotter, 2013). Dysbiosis is associated with many diseases, including irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD), celiac disease, multiple sclerosis, Sjogren's Syndrome, obesity, allergy, and diabetes (Carding et al., 2015; Marietta et al., 2020).

II. Related Policies

Policy Number	Policy Title
AHS-G2056	Diagnosis of Idiopathic Environmental Intolerance
AHS-G2061	Fecal Calprotectin Testing
AHS-G2121	Laboratory Testing for the Diagnosis of Inflammatory Bowel Disease

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) Prior to fecal microbiota transplant (FMT), fecal analysis by culture for the following microorganisms **MEETS COVERAGE CRITERIA:**
   a) Extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*
   b) Vancomycin-resistant *Enterococci* (VRE)
   c) Carbapenem-resistant *Enterobacteriaceae* (CRE)
   d) Methicillin-resistant *Staphylococcus aureus* (MRSA)

e) *Campylobacter*

f) *Shigella*

g) *Salmonella*

2) Prior to fecal microbiota transplant (FMT), fecal analysis for the following microorganisms by nucleic acid amplification testing (NAAT) **MEETS COVERAGE CRITERIA:**

a) *Clostridium difficile*

b) *Campylobacter*

c) *Salmonella*

d) *Shigella*

e) Shiga toxin-producing *Escherichia coli*

f) Norovirus

g) Rotavirus

h) COVID-19 (SARS-CoV-2)

3) Prior to fecal microbiota transplant (FMT), fecal analysis for the following microorganisms by nucleic acid amplification testing (NAAT) **DOES NOT MEET COVERAGE CRITERIA**:

a) Extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*

b) Vancomycin-resistant *Enterococci* (VRE)

c) Carbapenem-resistant *Enterobacteriaceae* (CRE)

d) Methicillin-resistant *Staphylococcus aureus* (MRSA)

e) Any other microorganisms not listed above

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

4) As a diagnostic test for the evaluation of intestinal dysbiosis, irritable bowel syndrome, malabsorption, **or** small intestinal overgrowth of bacteria, fecal analysis of the following components **DOES NOT MEET COVERAGE CRITERIA**:

a) Triglycerides

b) Chymotrypsin

c) Iso-butyrate, iso-valerate, and n-valerate

d) Meat and vegetable fibers

e) Long chain fatty acids

f) Cholesterol

g) Total short chain fatty acids

h) The levels of *Lactobacilli*, bifidobacteria, and *E. coli* and other "potential pathogens," including *Aeromona*, *Bacillus cereus*, *Campylobacter*, *Citrobacter*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Shigella*, *S. aureus*, *Vibrio*

i) For the identification and quantitation of fecal yeast (including *C. albicans*, *C. tropicalis*, *Rhodoptorul* and *Geotrichum*)

j) N-butyrate

k) Beta-glucoronidase

l) pH

m) Short chain fatty acid distribution (adequate amount and proportions of the different short chain fatty acids reflect the basic status of intestinal metabolism)

n) Fecal secretory IgA

IV. Table of Terminology

Term	Definition
ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
ASGE	American Society for Gastrointestinal Endoscopy
BSG	British Society of Gastroenterology
CBC	Complete blood cell count
CD	Crohn's disease
CDI	Clostridium difficile infection
CMS	Centers for Medicare and Medicaid Services
CPE	Carbapenemase-producing Enterobacteriaceae/Enterobacterales
CRE	Carbapenem-resistant Enterobacteriaceae/Enterobacterales
CRP	C-reactive protein
ECCO	European Crohn’s and Colitis Organization
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunoassay
EMA	Endomysial antibodies
EPEC	Enteropathogenic *Escherichia coli*
ESBL	Extended spectrum beta-lactamase
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
ESPID	European Society for Pediatric Infectious Diseases
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
FDA	Food and Drug Administration
FGFP	Flemish gut flora project
FMT	Fecal microbiota transplant
GI	Gastrointestinal

HIS	Healthcare Infection Society
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IDSA	Infectious Diseases Society of America
IMO	Intestinal methanogenic overgrowth
IND	Investigational new drug
MDROs	Multidrug resistant organisms
MRSA	Methicillin-resistant staphylococcus aureus
NAAT	Nucleic acid amplification testing
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
NICE	National Institute for Health and Care Excellence
SATs	Single-arm trials
SBBO	Small bowel bacterial overgrowth
SCFA	Short-chain fatty acids
SIBO	Small intestinal bacterial overgrowth
STEC	Shigatoxin-producing *Escherichia coli*
TTG	Tissue transglutaminase
UC	Ulcerative colitis
VRE	Vancomycin-resistant enterococci
WGO	World Gastroenterology Organization

V. Scientific Background

The human intestinal tract has a diverse and complex microbial community necessary for health and nutrition. The gut microbiome is estimated to consist of upwards of 1000 bacterial species (Guinane & Cotter, 2013; Ley, Peterson, et al., 2006; Qin et al., 2010). The microbiota functions with the immune system to protect against pathogens. It also performs essential metabolic functions, extracting certain forms of energy and nutrients from food and providing a source of other essential nutrients and vitamins (Carding et al., 2015).

The gut is colonized at birth, but the intestinal microbiome changes rapidly during the first year of life. In adults, each individual's unique population of gut microbiota is fairly stable over time; however, alterations in the microbiota can result from exposure to various environmental factors, including diet, toxins, drugs, and pathogens (Carding et al., 2015; Lozupone et al., 2012; Snapper & Abraham, 2022). This change in an individual's normal microbiota is called "dysbiosis" (Johnston Jr, 2023). Dysbiosis has been associated with obesity (Ley, Turnbaugh, et al., 2006; Zhang et al., 2009) malnutrition (Kau et al., 2011), systematic diseases such as diabetes (Qin et al., 2012) and chronic inflammatory diseases such as inflammatory bowel disease (IBD) (Frank et al., 2007; Guinane & Cotter, 2013). Both direct assessment of the gut microbiota (examination of bacteria levels) and indirect assessment (measurement of non-living markers such as pH or beta-glucoronidase) have been proposed for investigation of intestinal dysbiosis.

Microbial or microbial-derived components have also been cited as potential representations of dysbiosis. For example, short-chain fatty acids have been identified as a mechanism to regulate

intestinal processes and, as such, may represent dysbiosis (Johnston Jr, 2023). These fatty acids are the products of bacterial fermentation of fiber, and the concentrations of these fatty acids have been noted to decrease in IBD cases. Some fatty acids, especially butyrate, have been demonstrated to factor in signaling cascades that control immune function, which indicates a role in controlling intestinal inflammation (Parada Venegas et al., 2019). Ongoing research has uncovered many other potential links between intestinal metabolism and gut microbiota so many markers have been suggested as potential indicators of dysbiosis.

Many tests exist for the assessment of the gut microbiome. Due to the amount of conditions associated (or proposed to be associated) with gut microbiome balance, there are many corresponding tests, including screening measures intended for completely healthy individuals. These tests primarily revolve around nucleic acid amplification; microbial DNA or RNA is obtained from the sample, unique sequences are identified, and the nucleic acid is quantified (Raby, 2020). For instance, Viome offers a comprehensive screening panel that measures "all microorganisms" in the gut (including viruses, archaea, yeast, fungi, parasites, and bacteriophages). Those measurements are combined into a score for various issues, such as inflammatory activity, digestive efficiency, methane gas production, overall gas production, and more (Viome, 2023). Viome also provides a list of nutritional recommendations, broken down into individual foods. Viome performs RNA sequencing with Illumina NextSeq and uses bioinformatics algorithms to classify taxonomic data (Viome, 2019).

Some companies may offer companion products with their gut microbiome tests. BioHM provides a similar assessment of bacterial and fungal species in an individual's gastrointestinal tract, but the company also offers a series of probiotics. These probiotics are intended for various purposes, such as colon cleansing or immunity (BioHM, 2023). Other companies offering a gut microbiome test include Thryve, GenCove, DayTwo, American Gut, and Genova (DNATestingChoice, 2019; Genova, 2023).

The potential clinical impact of imbalance in the intestinal microbiota suggests a need for standardized diagnostic methods to facilitate microbiome profiling. Documenting dysbiosis has traditionally relied on classical microbiological techniques and the ability to culture pure isolates for identification and classification; however, the ability to classify bacteria and archaea according to individual 16S rRNA sequences can now possibly provide a rapid and detailed means of profiling complex communities of microorganisms (Casen et al., 2015; Zoetendal et al., 1998). Laboratory analysis of various fecal biomarkers have also been proposed as a method of identifying individuals with intestinal dysbiosis and may be useful in providing insight into the role of intestinal health and disease, and the development of non-gastrointestinal conditions associated with intestinal dysbiosis. However, there is a current lack of literature on the normal ranges of these biomarkers, which limit the applicability of these analyses in a general clinical setting (Bäckhed et al., 2012; Berry & Reinisch, 2013; Pang et al., 2014).

A technique revolving around restoring balance in a patient's microbiome is fecal microbiota transplantation (FMT). FMT is the infusion of stool from a healthy donor to a patient with presumed gut dysbiosis. The concept behind this technique is that the healthy donor's stool can facilitate a restoration of the ill patient's gut microbiome. This technique has seen some significant success in the treatment of *C. difficile* infections and may have potential applications in some other gastrointestinal or metabolic conditions such as IBD or IBS. As with any transplant procedure, there are several screening procedures that must be undertaken to minimize risk of

infection or other disease transmission. These screening procedures include evaluation of donor history, serum testing, and stool testing. The pathogens screened for in the donor's stool sample may vary between institutions, although some pathogens are universally screened for (such as enteric pathogens) (Kim & Gluck, 2019).

Clinical Utility and Validity

Falony et al. (2016) analyzed "two independent, extensively phenotyped cohorts: the Belgian Flemish Gut Flora Project (FGFP; discovery cohort; N = 1106) and the Dutch LifeLines-DEEP study (LLDeep; replication; N = 1135)." These two sets were integrated with global data sets, combining to yield 3948 items. A "core" set of 14 genera was identified. 69 clinical and questionnaire-based covariates were found to be associated with microbiota compositional variation with a 92% replication rate. The authors noted that "stool consistency showed the largest effect size, whereas medication explained largest total variance and interacted with other covariate-microbiota associations, but early-life events such as birth mode were not reflected in adult microbiota composition" (Falony et al., 2016).

Zhernakova et al. (2016) sequenced the gut microbiomes of 1,135 participants from a Dutch population-based cohort. The authors identified relations between the microbiome and "126 exogenous and intrinsic host factors, including 31 intrinsic factors, 12 diseases, 19 drug groups, 4 smoking categories, and 60 dietary factors." "Significant" associations were found between the gut microbiome and various intrinsic, environmental, dietary, medication parameters, and disease phenotypes. The authors calculated that 18.7% of variation in microbial composition could be explained by these factors, and they observed that fecal chromogranin A was exclusively associated with 61 microbial species, totaling 53% of the microbial composition. A more diverse microbiome was associated with low CgA concentrations. The authors concluded that "these results are an important step toward a better understanding of environment-diet-microbe-host interactions" (Zhernakova et al., 2016).

Lo Presti et al. (2019) profiled the fecal and mucosal microbiota of IBD and IBS patients. 38 IBD patients, 44 IBS patients, and 47 healthy controls were included, and overall, 107 fecal samples were provided. The authors found that "*Anaerostipes* and *Ruminococcaceae* were identified as the most differentially abundant bacterial taxa in controls, *Erysipelotrichi* was identified as [a] potential biomarker for IBS, while *Gammaproteobacteria*, *Enterococcus*, and *Enterococcaceae* [were identified] for IBD" (Lo Presti et al., 2019).

Malham et al. (2019) investigated the microbiotic profile of pediatric IBD. 143 IBD patients and 34 healthy controls were included. A reduced "richness" in microbiotic profile was observed in IBD patients compared to healthy controls. In ulcerative colitis (UC), that reduced richness was associated with high intestinal inflammation and extensive disease. Nine species were "significantly" associated with a healthy microbiome, and three species were associated with IBD. The authors remarked that the microbiome composition could differentiate between Crohn's Disease, UC, and healthy controls (Malham et al., 2019).

Danilova et al. (2019) compared the gut microbiome composition of IBD patients to healthy controls. 95 IBD patients and 96 healthy controls were included. The authors noted an increase of Proteobacteria and Bacteroidetes bacteria and decrease of Firmicutes bacteria and Euryarchaeota archaea in IBD patients. Butyrate-producing and hydrogen-utilizing bacteria were observed to have lower representation in IBD patients. Short-chain fatty acids (SCFA) were also

found to have a lower absolute content in IBD patients. The authors suggested that this finding may "indicate inhibition of functional activity and number of anaerobic microflora and/or an [*sic*] change in SCFA utilization by colonocytes" (Danilova et al., 2019).

Vaughn et al. (2018) in reviewing the current status of intestinal dysbiosis and fecal transplantation found that "it is hypothesized that intestinal dysbiosis may contribute to the pathogenesis of many diseases, especially those involving the gastrointestinal tract. Therefore, fecal microbiota transplantation (FMT) is increasingly being explored as a potential treatment that aims to optimize microbiota composition and functionality" (Vaughn et al., 2018). Holleran et al. (2018) also found that fecal transplant is not recommended for use outside of *Clostridium difficile* infection (CDI) due to concerns regarding outcome and safety; however, several case series and randomized controlled trials have described its use in a research environment for a few gastrointestinal conditions related to intestinal dysbiosis, including ulcerative colitis (UC), Crohn's disease (CD) and irritable bowel syndrome (IBS). The most successful reports of the clinical efficacy of FMT in gastrointestinal conditions outside of CDI have been in treating UC (Holleran et al., 2018).

Costello et al. (2019) evaluated fecal microbiota transplantation (FMT)'s efficacy on inducing remission in ulcerative colitis (UC). The authors compared anaerobically prepared donor FMT (n = 38) to autologous FMT (stool provided by patient themselves, n = 35). The primary outcome was defined as "steroid-free remission of UC… a total Mayo score of ≤2 with an endoscopic Mayo score of 1 or less at week 8." A total of 69 patients completed the trial, with the primary outcome being achieved in 12 of 38 donor FMT patients, compared to 3 of 35 receiving autologous FMT. Five of the 12 patients achieving the primary outcome in the "donor cohort" maintained remission at 12 months. The authors concluded that "in this preliminary study of adults with mild to moderate UC, 1-week treatment with anaerobically prepared donor FMT compared with autologous FMT resulted in a higher likelihood of remission at 8 weeks. Further research is needed to assess longer-term maintenance of remission and safety" (Costello et al., 2019).

Myneedu et al. (2019) performed a meta-analysis to evaluate whether fecal microbiota transplantation (FMT) was successful in treating IBS. A total of 8 single-arm trials (SATs, 90 patients total) and 5 randomized controlled trials (RCTs, 151 patients, 105 controls) were included. In the SAT cohort, the authors identified 59.5% of IBS patients demonstrating a significant improvement. In the RCT cohort, there were no significant differences between treatment and control cohorts, either by the IBS Severity Scoring System or the IBS Quality of Life (IBS-QOL). The authors concluded that "FMT was not effective in IBS. Variations in FMT methods and patient factors may contribute to the heterogeneous results of the trials" (Myneedu et al., 2019).

In a prospective survey-based study, Saha et al. (2021) studied the long-term safety profile of fecal microbiota transplantation (FMT) for recurrent C. *difficile* infection (CDI). 609 patients who underwent FMT were contacted at 1 week, 1 month, 6 months, 1 year and greater than 2 years after transplantation. Symptoms and new medical diagnosis were recorded at each time point. Less than 1 year after FMT, greater than 60% of patients had diarrhea and 19-33% had constipation. At 1 year, 9.5% of patients reported additional CDI episodes. Additionally, patients with IBD, dialysis dependent kidney disease, and multiple FMTs had a higher risk of diarrhea. When patients were followed up after 2 years post-FMT, 73 new diagnoses were reported

including gastrointestinal disorders (13%), weight gain (10%), and new infections unrelated to FMT (11.8%). The median time for new infections post-FMT was 29 months. The authors conclude that FMT "appears safe with low risk of transmission of infections. Several new diagnoses were reported, which should be explored in future studies" (Saha et al., 2021).

In a 12-week double-blind placebo-controlled pilot trial, Yu et al. (2020) studied the use of FMT to improve metabolic outcomes in obese patients. From a total of 24 patients, 12 adults with obesity and mild to moderate insulin resistance were given weekly oral FMT capsules from healthy lean donors and 12 adults were given. At 0, 6, and 12 weeks, various metabolic parameters were measured including HbA1c, body weight, body composition, and resting energy expenditure. According to the results, there were no significant differences between the two groups in glycemic outcomes, weight, or body composition over the 12-week period. There was a minor improvement in HbA1c after FMT as compared to placebo. These results suggest "that intestinal microbial manipulation by FMT capsules does not meaningfully alter human metabolism and weight in adults with obesity" (Yu et al., 2020).

Macareño-Castro et al. (2022) conducted a systematic review on the use of FMT on Carbapenem-resistant Enterobacteriaceae. In using 10 studies with a combination of both retrospective and prospective cohorts, they found that among 112 FMT recipients with confirmed CRE, 78.7% of patients experienced CRE decolonization at the end of study follow-up (6-12 months). The predominant strains reported were *Klebsiella pneumoniae* and *Escherichia coli*. The researchers also reported that there were no “severe complications even in immunosuppressed patients and in those with multiple underlying conditions.” This overall supports the clinical utility of FMT for CRE, but requires more studies, such as randomized trials, to validate the safety and reliable use for complete bacterial eradication.

VI. Guidelines and Recommendations

World Gastroenterology Organization (WGO) Global Guidelines

The WGO published guidelines on functional gastrointestinal (GI) symptoms. In it, they identify diagnostic tests for these symptoms. The basic diagnostic tests are as follows:

- Complete blood cell count (CBC)
- Erythrocyte sedimentation rate (ESR) / C-reactive protein (CRP)
- Biochemistry panel
- Fecal occult blood (patient aged > 50 y)
- Pregnancy test
- Liver function tests
- Calprotectin or other fecal test to detect inflammatory bowel disease in patients thought to have IBS, but in whom inflammatory bowel disease (IBD) is a possibility; now routine in many primary care settings (in the United Kingdom)
- Celiac serology; considered routine in areas with a high prevalence of celiac disease
- Stool testing for ova and parasites (Hunt et al., 2014)

The WGO also released their global guidelines for Inflammatory Bowel Disease in 2015 (published in 2016). Their recommendations concerning stool examination and testing are as follows:

- "Routine fecal examinations and cultures should be carried out to eliminate bacterial, viral, or parasitic causes of diarrhea."
- "Testing for *Clostridium difficile* (should be considered even in the absence of antecedent antibiotics) — should be carried out within 2 hours of passage of stools."
- "A check for occult blood or fecal leukocytes should be carried out if a patient presents without a history of blood in the stool, as this can strengthen the indication for lower endoscopy. Where lower endoscopy is readily available, these tests are rarely indicated."
- "Lactoferrin, α1-antitrypsin. The main reason for listing this test is to rule out intestinal inflammation, rather than using it as a positive diagnostic test. It may not be available in developing countries, but it can be undertaken relatively inexpensively and easily with rapid-turnaround slide-based enzyme-linked immunoassay (ELISA) tests."
- "Calprotectin — a simple, reliable, and readily available test for measuring IBD activity — may be better for UC than CD; the rapid fecal calprotectin tests could be very helpful in developing countries. If available, a home test may be useful as a routine for follow-up" (Bernstein et al., 2016).

American Gastroenterological Association (AGA)

The AGA published a review to "describe key principles in the diagnosis and management of functional gastrointestinal (GI) symptoms in patients with inflammatory bowel disease". In it, they include the following relevant items:

- "Alternative pathophysiologic mechanisms should be considered and evaluated (small intestinal bacterial overgrowth, bile acid diarrhea, carbohydrate intolerance, chronic pancreatitis) based on predominant symptom patterns."
- "Until further evidence is available, fecal microbiota transplant should not be offered for treatment of functional GI symptoms in IBD."
- "In a recent cross-sectional analysis, no association was observed between IBS symptoms and microbiome alterations among patients with IBD although effects of confounding could not be excluded" (Colombel et al., 2019).

The AGA published guidelines on FMT, including information on donor pathogen screening. *C. difficile* toxin B and culture for enteric pathogens were "suggested" to be screened for, *Giardia*, *Cryptosporidium*, *Isospora* and *Cyclospora*, *Listeria*, *E. coli* O157, *Vibrio*, and *Norovirus* should be "considered", and Cytomegalovirus, Human T-cell lymphoma virus, Epstein–Barr virus, *Dientamoeba fragilis*, *Blastocystis hominis*, *Strongyloides stercoralis*, *Entamoeba histolytica*, *H. pylori*, *Schistosoma*, JC virus, Vancomycin-resistant *enterococci*, and Methicillin-resistant *Staphylococcus aureus* should "maybe" [term used by authors] be screened (Kelly et al., 2015).

American College of Gastroenterology (ACG)

The ACG published a guideline regarding the management of Crohn's Disease. In it, they recommend that "In patients who have symptoms of active Crohn's disease, stool testing should be performed to include fecal pathogens, *Clostridium difficile* testing, and may include studies that identify gut inflammation such as a fecal calprotectin" (Lichtenstein et al., 2018).

The ACG also published a guideline regarding management of ulcerative colitis. In it, the ACG writes that "FMT requires more study and clarification of treatment before use as a therapy for UC [ulcerative colitis]." The ACG comments that the variability across all steps of the procedure (donor screening, delivery, treatment duration, et al.) makes interpretation of the current results "difficult". Finally, the ACG notes that some institutions have been using "comprehensive intestinal pathogen testing through PCR-based assays that include many bacterial and viral pathogens," but that the "prevalence and impact of non–C. diff intestinal pathogens detected through such assays remain to be robustly established" (Rubin et al., 2019).

ACG published a guideline regarding management of irritable bowel syndrome. ACG does not recommend the use of fecal transplant for the treatment of global IBS symptoms. "Evidence to support FMT for the treatment of IBS is limited and of very low quality and thus cannot be recommended at present" (Lacy et al., 2021).

ACG published a guideline regarding use of FMT in recurrent and severe C. *difficile* infection. ACG suggests considering FMT for "patients with severe and fulminant CDI refractory to antibiotic therapy, in particular, when patients are deemed poor surgical candidates. For patients experiencing their second or further recurrence of CDI, FMT can be delivered to prevent further recurrences through capsule or colonoscopy. Enema may be used if other methods are unavailable." ACG suggests "repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT. FMT should be considered for recurrent CDI in patients with IBD" (Kelly et al., 2021).

European Crohn's and Colitis Organization (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR)

These joint guidelines include some relevant items on inflammatory bowel disease (IBD), which includes both Crohn's disease (CD) and ulcerative colitis (UC). These items include:

- "At diagnosis, every patient should have a biochemical assessment with full blood count, inflammatory markers (C-reactive protein [CRP])… and a stool sample for microbiological analysis, including *C. difficile*."
- "Stool specimens should be obtained to exclude common pathogens and specifically assayed for C difficile toxin." (Maaser et al., 2019)

2012 Rome Foundation Report

An international Working Group convened in 2012 "to provide clinical guidance on modulation of gut microbiota in IBS" and released their findings on intestinal microbiota in functional bowel disorders: a Rome foundation report in 2013. They state the following "Diagnostic and therapeutic general recommendations":

- "There is currently no clinically useful way of identifying whether the microbiota are disturbed in particular patients with irritable bowel syndrome (IBS).
- Dietary evaluation and exclusion of possible sources of unabsorbable carbohydrates including fermentable oligo-, di- and mono-saccharides and polyols and excessive fibre could be beneficial in select patients.

- Probiotics have a reasonable evidence base and should be tried, for a period of at least 1 month, at adequate doses before a judgement is made about the response to treatment.
- The utility of testing for small intestinal bacterial overgrowth (SIBO) in the setting of IBS remains an area of uncertainty.
- If SIBO is strongly suspected based on clinical presentation and testing is being considered, using stringent criteria for the glucose breath test or jejunal aspirate appear to be the best tests.
- Consideration should be given to discontinuing proton pump inhibitors in those with SIBO.
- There is emerging evidence that non-absorbable antibiotics may have the potential to reduce symptoms in some patients with IBS" (Simren et al., 2013).

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases (ESPGHAN/ESPID)

These joint guidelines reviewed management of acute gastroenteritis (AGE) in children. In it, they note that AGE does not require a specific diagnostic workup and that "microbiological investigation is not helpful in most cases." Fecal markers are also not recommended for differentiating viral and bacterial AGE. However, the guidelines observe that "microbiological investigations may be considered in children with underlying chronic conditions (eg, oncologic diseases, IBDs, etc), in those in extremely severe conditions, or in those with prolonged symptoms in whom specific treatment is considered" (Guarino et al., 2014).

National Institute for Health and Care Excellence (NICE)

NICE updated their IBS guidelines in 2017. In it, they list the following items about diagnostic tests:

"In people who meet the IBS diagnostic criteria, the following tests should be undertaken to exclude other diagnoses:

- full blood count (FBC)
- erythrocyte sedimentation rate (ESR) or plasma viscosity
- c-reactive protein (CRP)
- antibody testing for coeliac disease (endomysial antibodies [EMA] or tissue transglutaminase [TTG]).

The following tests are not necessary to confirm diagnosis in people who meet the IBS diagnostic criteria:

- ultrasound
- rigid/flexible sigmoidoscopy
- colonoscopy; barium enema
- thyroid function test
- faecal ova and parasite test
- faecal occult blood
- hydrogen breath test (for lactose intolerance and bacterial overgrowth)" (NICE, 2017).

British Society of Gastroenterology (BSG)

The BSG published a guideline on the investigation of chronic diarrhoea in adults. Relevant items include:

- For malabsorption, fecal tests have not received "significant support" in publications and have not "established themselves in clinical practice outside specialist centres."
- "We suggest culture of small bowel aspirates as it is the most sensitive test for small bowel bacterial overgrowth (SBBO), but methods are poorly standardized and positive results may not reflect clinically significant SBBO… in the absence of an optimal test to confirm the presence of bacterial overgrowth and in those with a high test probability of SBBO, we recommend an empirical trial of antibiotics; the value of this approach has not been subject to definitive study."
- "We recommend faecal elastase testing as the preferred non-invasive test for pancreatic function" (Arasaradnam et al., 2018).

The BSG also published an extensive guideline on the management of Inflammatory Bowel Disease (including both ulcerative colitis (UC) and Crohn's disease) in adults. Their relevant comments and recommendations include:

- "In patients presenting with suspected UC, stool cultures and *Clostridium difficile* toxin assay should always be performed to rule out infective causes."
- "Ileocolonoscopy with biopsy is established as the first-line investigation for suspected Crohn's disease."
- "We recommend that all patients presenting with acute flares of colitis should have stool cultures for enteroinvasive bacterial infections and stool *Clostridium difficile* assay."
- "In spite of these encouraging data, FMT [Faecal microbial transplantation] remains an investigational treatment for use only in clinical trials in IBD."
- "There is currently no place for FMT in the management of IBD unless complicated by *C. difficile* infection outside of the clinical trial setting" (Lamb et al., 2021).

British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS)

This joint guideline was published to provide guidance on "the use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications." These guidelines include a list of items that should be screened for potential stool donors, which are as follows:

- "*Clostridium difficile* PCR"
- *"Campylobacter*, *Salmonella*, and *Shigella* by standard stool culture and/ or PCR"
- "Shiga toxin-producing *Escherichia coli* by PCR"
- "Multi-drug resistant bacteria, at least CPE [*carbapenemase-producing Enterobacteriaceae*] and ESBL [extended spectrum beta-lactamase]"
- "Stool ova, cysts and parasite analysis, including for Microsporidia"
- "Faecal antigen for *Cryptosporidium* and *Giardia"*
- "Acid fast stain for *Cyclospora* and *Isospora"*
- *"Helicobacter pylori* faecal antigen"
- "Norovirus, rotavirus PCR."

The above list is for stool screening. A separate list is provided for serum screening. The guideline also recommends that "donors should have successfully completed a donor health questionnaire and laboratory screening assays both before and after the period of stool donation" (Mullish et al., 2018).

Infectious Diseases Society of America/American College of Gastroenterology/American Society for Gastrointestinal Endoscopy/American Gastroenterological Association/North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (IDSA/ACG/ASGE/AGA/NASPGHAN)

These joint guidelines were sent to the FDA regarding recurrent *Clostridium difficile* infection (CDI). In it, the guidelines recommend screening donors for fecal microbiota transplantation (FMT) for *C. difficile* toxin B and performing a culture for enteric pathogens (IDSA/ACG/ASGE/AGA/NASPGHAN, 2013).

NASPGHAN published an FMT guideline for children in 2019, and the same analytes for screening (C difficile toxin B, culture for enteric pathogens) were recommended (Davidovics et al., 2019).

An addendum was published to the 2019 guidelines due to the 2019 FDA Safety Warning regarding FMT. In it, the following recommendation was made: "FMT donor stool screening should include (but not be limited to) MDRO testing for spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, vancomycin-resistant *Enterococci* (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE), and methicillin-resistant *Staphylococcus aureus* (MRSA). Donors and/or stools positive for MDROs should not be used for FMT" (Michail et al., 2020).

Food and Drug Administration (FDA)

The FDA has issued a guidance statement for fecal microbiota transplant (FMT) stating that it will exercise enforcement discretion regarding the investigational new drug (IND) requirements for the use of fecal microbiota for transplantation. In 2019, the FDA updated their guidance on FMT, stating that "FMT donor stool testing must include MDRO testing to exclude use of stool that tests positive for MDRO. The MDRO tests should at minimum include extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae (CRE), and methicillin-resistant Staphylococcus aureus (MRSA). Culture of nasal or peri-rectal swabs is an acceptable alternative to stool testing for MRSA only. Bookend testing (no more than 60 days apart) before and after multiple stool donations is acceptable if stool samples are quarantined until the post-donation MDRO tests are confirmed negative" (FDA, 2019).

In an April 2020 update, the FDA addressed the topic of fecal microbiota transplantation within the context of the 2020 COVID-19 outbreak. The FDA included additional protections regarding stool donation and donor screening, which are as follows:

- "Stool donor screening, including an assessment of whether, since December 1, 2019, the donor was diagnosed with laboratory-confirmed SARS-CoV-2 infection, experienced symptoms of COVID-19 (e.g., fever, cough, shortness of breath) not explained by another diagnosis, or was exposed to a suspected or confirmed case of COVID-19 or SARS-CoV-2 infection."

- "Testing of the stool donation or stool donor for SARS-CoV-2 virus or RNA. Testing approaches might include testing upper respiratory specimens (e.g., nasal swabs) or other specimens (e.g., rectal swabs or stool donations)" (FDA, 2020a).

In a March 2020 update, the FDA addressed the potential risk of infections with the use of FMT. The FDA advises that "patients considering FMT for the treatment of *C. difficile* infection should speak to their health care provider to understand the associated risks" (FDA, 2020b). The FDA is aware of infections caused by enteropathogenic *Escherichia coli* (EPEC) and *Shigatoxin-producing Escherichia coli* (STEC) that have occurred following investigational use of FMT (FDA, 2020b).

Fecal Microbiota Transplantation Workgroup (2011)

This Working Group published guidelines on FMT. Fecal donor screening recommendations were included. The following analytes were recommended to be screened:

- "*C difficile* toxin B by PCR; if unavailable, then evaluation for toxins A and B by enzyme immunoassay (EIA)
- Routine bacterial culture for enteric pathogens
- Fecal Giardia antigen
- Fecal Cryptosporidium antigen
- Acid-fast stain for Cyclospora, Isospora, and, if antigen testing unavailable, Cryptosporidium
- Ova and parasites
- *Helicobacter pylori* fecal antigen (for upper gastrointestinal [GI] routes of FMT administration)" (Bakken et al., 2011).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of

1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
82239	Bile acids; total
82542	Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen
82705	Fat or lipids, feces; qualitative
82710	Fat or lipids, feces; quantitative
82715	Fat differential, feces, quantitative
82725	Fatty acids, nonesterified
82784	Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83630	Lactoferrin, fecal; qualitative
83986	pH; body fluid, not otherwise specified
84311	Spectrophotometry, analyte not elsewhere specified
87045	Culture, bacterial; stool, aerobic, with isolation and preliminary examination (eg, KIA, LIA), Salmonella and Shigella species
87046	Culture, bacterial; stool, aerobic, additional pathogens, isolation and presumptive identification of isolates, each plate
87075	Culture, bacterial; any source, except blood, anaerobic with isolation and presumptive identification of isolates
87102	Culture, fungi (mold or yeast) isolation, with presumptive identification of isolates; other source (except blood)
87177	Ova and parasites, direct smears, concentration and identification
87209	Smear, primary source with interpretation; complex special stain (eg, trichrome, iron hemotoxylin) for ova and parasites
87328	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; cryptosporidium
87329	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; giardia
87336	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; Entamoeba histolytica dispar group
87493	Infectious agent detection by nucleic acid (DNA or RNA); Clostridium difficile, toxin gene(s), amplified probe technique
87500	Infectious agent detection by nucleic acid (DNA or RNA); vancomycin resistance (eg, enterococcus species van A, van B), amplified probe technique

CPT	Code Description
87641	Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus, methicillin resistant, amplified probe technique
87798	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism
89160	Meat fibers, feces
S3708	Gastrointestinal fat absorption study

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X. Revision History

Revision Date	Summary of Changes
09/06/2023	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity: Addition of ":" at the end of the main body of CC1 and CC2.