Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Fecal Microbiota Transplantation (Fecal Bacteriotherapy)

Description/Background

FECAL MICROBIOTA

Fecal microbiota transplantation (FMT) involves the infusion of intestinal microorganisms via transfer of stool from a healthy individual into a diseased patient, with the intent of restoring normal intestinal flora. The stool can be infused as a liquid suspension into a patient's upper gastrointestinal tract through a nasogastric tube or gastroscopy, or the stool can be infused into the colon through a colonoscope or rectal catheter, or administered orally via capsules (i.e., encapsulated FMT).

The goal of FMT is to replace damaged and/or disordered native microbiota with a stable community of donor microorganisms. The treatment is based on the premise that an imbalance in the community of microorganisms residing in the gastrointestinal tract (i.e., dysbiosis) is associated with specific disease states, including susceptibility to infection.

The human microbiota, defined as the aggregate of microorganisms (bacteria, fungi, archaea) on and in the human body, is believed to consist of approximately 10-100 trillion cells, approximately 10 times the number of human cells. Most human microbes reside in the intestinal tract and most of these are bacteria. In its healthy state, intestinal microbiota perform a variety of useful functions including aiding in the digestion of carbohydrates, mediating the synthesis of certain vitamins, repressing growth of pathogenic microbes, and stimulating the lymphoid tissue to produce antibodies to pathogens.

Applications

Clostridioides difficile Infection

To date, the major potential clinical application of FMT is treatment of *Clostridioides difficile* infection (CDI). Infection of the colon with *C difficile* is a major cause of colitis and can cause life-threatening conditions including colonic perforation and toxic megacolon. *C difficile* occurs naturally in intestinal flora. According to the 2019 Centers for Disease Control and Prevention (CDC) report, *Antibiotic Resistance Threats in the United States,* CDI continues to be an urgent threat. The crude

overall incidence rate of CDI in 2019 was 121.2 cases per 100,000 persons.[1] In 2017, there were an estimated 223,900 cases of CDI in hospitalized patients and an estimated 12,900 CDI-associated deaths. Interestingly, the overall number of cases of healthcare-associated CDI cases has been trending down since 2012 when the number of cases was estimated at 251,400.

It is unclear what causes *C difficile* overgrowth, but disruption of the normal colonic flora in conjunction with colonization by *C difficile* are major components. Disruption of the normal colonic flora occurs most commonly following administration of oral, parenteral or topical antibiotics. Standard treatment for CDI is antibiotic therapy. However, symptoms recur in up to 35% of patients and up to 65% of patients with recurrences develop a chronic recurrent pattern of CDI.[2]

Other Applications
Other potential uses of FMT include treatment of conditions in which altered colonic flora may play a role. These include inflammatory bowel disease, irritable bowel syndrome, idiopathic constipation and non-gastrointestinal disease such as multiple sclerosis, obesity, autism and chronic fatigue syndrome. However, for these conditions, the contribution of alterations in colonic flora to the disorder is uncertain or controversial.

There is interest in alternatives to human feces that might have the same beneficial effects on intestinal microbiota without the risks of disease transmission. A proof of principle study was published in 2013 that evaluated a synthetic stool product in 2 patients with recurrent CDI.[3] The product is made from 33 bacterial isolates that were developed from culturing stool from a healthy donor.

Regulatory Status:

In 2022, the U.S. Food and Drug Administration (FDA) issued updated draft guidance on investigational new drug requirements for the use of FMT to treat CDI not responsive to medication therapy.[4] The draft guidance is similar to the 2013 guidance and states that the FDA is continuing to consider how to regulate FMT and that, during this interim period, the agency will use enforcement discretion regarding the use of fecal transplant to treat treatment-resistant CDI. The FDA requires that physicians obtain adequate informed consent from patients or their legal representative before performing the intervention. The document also noted that selective enforcement does not apply to the use of fecal transplant for treating conditions other than treatment-resistant CDI.

In 2019, the FDA issued a safety alert regarding the use of FMT due to the potential risk of serious or life-threatening infections caused by the transmission of multi-drug resistant organisms (MDROs).[5] Two immunocompromised individuals received investigational FMT and developed invasive infections caused by the transmission of extended-spectrum beta-lactamase-producing Escherichia coli. One of the affected individuals died. The donor stool used in each patient's FMT procedures had not been tested for extended-spectrum beta-lactamase-producing gram-negative organisms prior to use. Follow-up testing verified donor stool was positive for MDROs identical to the organisms isolated from the two patients. Due to these events, the FDA has determined that the following additional protections are required for any investigational use of FMT:

- Donor screening that specifically addresses risk factors for colonization with MDROs and exclusion of individuals at higher risk of colonization with MDROs (e.g., health care workers, persons who have recently been hospitalized or discharged from long-term care

facilities, persons who regularly attend outpatient medical or surgical clinics, and persons who have recently engaged in medical tourism).
- MDRO testing of donor stool and exclusion of stool testing positive for MDROs. At a minimum, tests should include:
    - extended-spectrum beta-lactamase-producing Enterobacteriaceae
    - vancomycin-resistant enterococci
    - carbapenem-resistant Enterobacteriaceae
    - methicillin-resistant Staphylococcus aureus
- All FMT products currently in storage for future use must be quarantined until donor MDRO carriage risk can be assessed and FMT products are tested and found negative for MDROs.
- The informed consent process for FMT treatment subjects should describe the risk of MDRO transmission and infection and the measures being implemented for donor screening and stool testing.

November 2022, the FDA approved the first commercial FMT product, RBX2660 (Rebyota™)[6], for prevention of recurrent CDI in adults. Prepared from donor stool, each dose is administered rectally. Like standard FMT stool suspensions, the precise mixture of microbes in RBX2660 is undefined.

April 2023, the FDA approved SER-109 (Vowst™)[7], the first fecal microbiota product that is taken orally. Vowst is approved for the prevention of recurrence of C. difficile infection (CDI) in individuals 18 years of age and older, following antibacterial treatment for recurrent CDI.

Medical Policy Statement

The safety and effectiveness of fecal microbiota transplant (FMT) have been established. It may be considered a useful therapeutic option when indicated for individuals with active recurrent Clostridioides difficile infection meeting selection criteria.

NOTE: For criteria for the prevention of recurrence of CDI in individuals following antibiotic treatment for recurrent CDI, see pharmacy policies on FDA approved products for this indication.

Inclusionary and Exclusionary Guidelines

Inclusions:
Fecal microbiota transplantation **using a compounded product*** may be considered **established** for the treatment of individuals with recurrent Clostridioides difficile infection when **ALL** the following criteria are met:

- There is an incident case of Clostridioides difficile that is treated with standard antibiotic C. difficile infection (CDI) therapy,
- There have been at least 2 recurrences** that are refractory to standard antibiotic treatment.
- The physicians obtain adequate informed consent from patients or their legal representative before performing the intervention,
- The providers perform appropriate screening and testing of the stool donor and stool,
- Procedures that mitigate potential safety concerns of FMT are followed.

* A compounded product refers to an FMT product not involving a stool bank where the FDA exercises enforcement discretion with respect to applicable investigational new drug (IND) requirements. For example, this may include FMT products prepared in a hospital laboratory under the direction of licensed health care providers for the purpose of treating their patients provided

**A recurrence occurs within 8 weeks of the completion of a course of *C. difficile* infection (CDI) therapy.

Fecal microbiota transplantation **using a Food and Drug Administration (FDA)-approved product** may be considered **established** for the treatment of individuals with recurrent Clostridioides difficele infection when the following criteria are met:

- There have been at least 2 recurrences that are refractory to standard antibiotic treatment, **AND**
- The recipient is 18 years of age or older.

A **repeat** fecal microbiota transplant (FMT) is considered established in individuals who experience a recurrence of *Clostridioides difficile* infection within 8 weeks of an initial FMT.

Exclusions:

- Fecal microbiota transplantation that does not meet the criteria in inclusions (e.g., when used as first-line treatment; when used for other indications, such as inflammatory bowel disease, autoimmune disease, etc.).

NOTE: Due to the potential for serious adverse reactions with FMT, the U.S. Food and Drug Administration (FDA) has determined that the following protections are needed for use of FMT:

1. Donor screening with questions that specifically address risk factors for colonization with multi-drug resistant organisms (MDROs), and exclusion of individuals at higher risk of colonization with MDROs.
2. MDRO testing of donor stool and exclusion of stool that tests positive for MDRO. FDA scientists have determined the specific MDRO testing and frequency that should be implemented.
3. Consent for the use of FMT is obtained from the individual or a legally authorized representative in accordance with FDA guidance.
4. Screening and testing procedures are performed per FDA recommendations for both SARS-CoV-2 and monkeypox viruses.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

44705	G0455*	44799	0780T

**G0455 is used for Medicare only*

Procedure may be billed with:

43753	45330	45378

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Recurrent *Clostridioides difficile* Infection
Fecal Microbiota Transplantation (not commercially available)

Clinical Context and Test Purpose
The purpose of fecal microbiota transplantation (FMT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with recurrent *Clostridioides difficile* infection (CDI) refractory to antibiotic therapy.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with recurrent CDI refractory to antibiotic therapy.

Interventions
The therapy being considered is FMT with a product that is not commercially available.

Comparators
The following therapy is currently being used to treat CDI: standard antibiotic regimens.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Outcomes reported in FMT trials for CDI include clinical cure, resolution of CDI with no further recurrence, or reduced risk of CDI recurrence. There are inconsistencies across these

trials in how CDI resolution (i.e., treatment success) and recurrence are defined and measured.[8,9] Treatment success generally required a resolution of diarrhea symptoms with or without laboratory confirmation; up to 3 consecutive negative stool tests for *C. difficile* toxin have been required to define cure in 1 trial. Conversely, recurrence generally required the presence of diarrhea with or without laboratory confirmation or the need for further treatment for up to 17 weeks after the incident case. The 2017 Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines for CDI recommend against repeat testing for *C. difficile* toxin during the same episode of diarrhea or for asymptomatic patients, since >60% of patients may remain positive for the *C. difficile* toxin even after successful treatment.[10] Per the guidelines, a recurrent case occurs within 2 to 8 weeks of the incident case and requires both clinical plus laboratory evidence of disease for diagnosis. The 2021 update to the IDSA/SHEA guideline does not comment on repeat testing nor does it provide an updated definition of recurrent CDI.[10,] Per 2 separate 2021 guidelines from the American Society of Colon and Rectal Surgeons (ASCRS) and American College of Gastroenterology (ACG), a recurrent case occurs within 8 weeks after the completion of a course of CDI therapy and requires both clinical plus laboratory evidence of disease for diagnosis.[12,13,]

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A 2023 Cochrane review by Minkoff et al compared donor FMT (dFMT) to control for the management of recurrent CDI in immunocompetent individuals.[14,] Six RCTs were included (N=320); the route of administration was the upper gastrointestinal tract via a nasoduodenal tube in 1 study, enema only in 2 studies, colonoscopic only in 2 studies, and either nasojejunal or colonoscopic delivery in 1 study. The controls included vancomycin (5 studies), fidaxomicin (1 study), autologous FMT (aFMT]) (1 study), and rectal bacteriotherapy (1 study). Results demonstrated that dFMT significantly increased the likelihood of recurrent CDI resolution when compared to control (risk ratio, 1.92; 95% confidence interval [CI], 1.36 to 2.71; p=.02). The risk of serious adverse events did not differ between dFMT and control groups (risk ratio, 0.73; 95% CI, 0.38 to 1.41), nor did the risk of mortality (risk ratio, 0.57; 95% CI, 0.22 to 1.45).

Rokkas et al (2019) performed a systematic review and meta-analysis to assess the efficacy of FMT for the treatment of recurrent CDI.[9] Six RCTs were included in the analysis (N=348), and 7 interventions were compared (donor FMT [dFMT], autologous FMT [aFMT], vancomycin, vancomycin plus dFMT, vancomycin plus bowel lavage, fidaxomicin, and placebo). The primary outcome was the resolution of CDI-related symptoms. The network meta-analysis demonstrated that dFMT was superior to vancomycin (odds ratio [OR], 20.02; 95% credible interval [CrI], 7.05 to 70.03), vancomycin plus dFMT (OR, 4.69; 95% CrI, 1.04 to 25.22), vancomycin plus bowel lavage

(OR, 22.77; 95% CrI, 4.34 to 131.63), and fidaxomicin (OR, 22.01; 95% CrI, 4.38 to 109.63) groups.

Tariq et al (2019) performed a systematic review and meta-analysis to assess the efficacy of FMT as a treatment option for recurrent CDI on the basis of results from open-label studies and placebo-controlled clinical trials.[8] The authors were motivated to perform this analysis based on observations that FMT cure rates for CDI are high in observational studies (e.g., >90%) but appear to be consistently lower in open-label studies and clinical trials. Thirteen studies were included for evaluation, including six placebo-controlled RCTs and seven open-label studies. Out of 610 patients receiving FMT, 439 patients achieved clinical cure (76.1%; 95% confidence interval [CI]: 66.4% to 85.7%); study heterogeneity was significant (I^2 =91.35%). Cure rates were found to be lower in randomized trials (139/216, 67.7%; 95% CI: 54.2% to 81.3%) vs. open-label studies (300/394, 82.7%; 95% CI: 71.1% to 94.3%; p < 0.001). Subgroup meta-analysis by FMT route of administration indicated lower cure rates with enema than colonoscopy (66.3% vs. 87.4%; p < 0.001). However, no differences between colonoscopy and oral delivery were detected (87.4% to 81.4%; p= 0.17). Lower cure rates were observed for studies that included both recurrent and refractory CDI than those that only included patients with recurrent CDI (63.9% vs. 79%; p < 0.001).

Khan et al (2018) conducted a systematic review of the literature and meta-analysis of pooled data on the use of FMT as a treatment option for recurrent CDI.[15] Reviewers only selected RCTs comparing FMT (fresh or frozen) with medical treatment. Among the selected studies, there was a nonsignificant trend toward the resolution of diarrhea following a single fresh FMT infusion compared with frozen FMT or medical treatment (odds ratio, 2.45; 95% confidence interval [CI], 0.78 to 7.71; p=0.12, I^2=69%), but different forms and routes of FMT administration were shown to be equally efficacious. Reviewers concluded that FMT is a promising treatment modality for recurrent CDI. Variability of FMT dose usages, small trial populations, and window to assess treatment success or failure limited analysis data.

In 2017, Quraishi et al published a systematic review and meta-analysis of 7 RCTs comparing FMT with standard antibiotic regimen in 1973 patients with recurrent and refractory CDI (follow-up, 10-13 weeks), and 30 case series (sample sizes ≥10 patients) describing the effect of FMT in 1545 patients with recurrent and refractory CDI.[16] Reviewers deemed the 7 RCTs as having a low risk of bias (including adequate randomization with allocation concealment and intention-to-treat analysis). Reviewers did not report an assessment of bias in terms of blinding, sample size adequacy, or possible differences in baseline characteristics. They argued that none of trials examining the efficacy of FMT were true placebo controlled, and the 30 case series followed patients until resolution of CDI (range, 10 weeks to 8 years), though some had incomplete follow-up. In the pooled analysis, 92% of patients had a resolution of CDI (95% confidence interval [CI], 89% to 94%); heterogeneity were classified as likely moderate (I^2=59%). Additionally, in the 7 trials that evaluated FMT, the intervention overall was associated with an increase in the resolution of recurrent and refractory CDI (relative risk [RR], 0.23; 95% CI, 0.07 to 0.80). The 30 case series reported resolution rates for CDI from 68% to 100%.

The Quraishi et al (2017) review found FMT to be effective in the treatment of recurrent and refractory CDI, and no serious adverse events from FMT were reported in the RCTs through the follow-up period. Most adverse effects in the case series were minor (bloating, belching, abdominal cramps, pain or discomfort, nausea, vomiting, excess flatulence, constipation, transient fever, urinary tract infections, self-limiting diarrhea, irregular bowel movement). However,

reviewers noted several limitations. Based on variability in the definitions of CDI resolution used across the studies, reviewers could not distinguish between recurrent and refractory CDI. There were also variations across studies in terms of recipient preparations, number of infusions, time to resolution, follow-up, overall response, dosing, concurrent use of medications, and other nonspecified biases. Heterogeneity among studies was considerable.

Prior to the availability of RCTs in this arena, several systematic reviews of uncontrolled studies on fecal microbiota transplantation for treating CDI have been published.[17-20]Overall, data from these uncontrolled studies have reported high rates of resolution of recurrent CDI following treatment with FMT.

Table 1 summarizes the characteristics of selected systematic reviews.

Table 1. Characteristics of Systematic Review

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Minkoff et al (2023)	To 2022	6	Recurrent CDI treated with donor FMT, standard of care therapies, or autologous FMT	320	Open-label and blinded RCTs	8 to 17 weeks
Rokkas et al (2019)	To 2018	6	Recurrent CDI treated with FMT, standard of care therapies, or placebo	348	Open-label and blinded RCTs	8 to 17 weeks
Tariq et al (2019)	To 2017	13	Recurrent or refractory CDI treated with FMT or placebo	Total: 768 (20 to 179) FMT: 610 (16 to 179) Placebo: 157 (14 to 44)	Open-label, randomized trials with no control group, and placebo-controlled RCTs	NR to 17 weeks
Khan et al (2018)	To 2018	7	Recurrent CDI treated with FMT	543 (20 to 178)	RCTs	NR
Quraishi et al (2017)	To 2016	37	Recurrent or refractory CDI treated with FMT	3518 (NR)	7 RCTs, 30 case series	10 weeks to 8 years

CDI: *Clostridioides difficile* infection; FMT: fecal microbiota transplantation; NR: not reported.

Retrospective Studies

Investigating the long-term clinical outcomes of FMT in patients with CDI, Mamo et al (2018) conducted a retrospective study using a follow-up survey of 137 patients who had received FMT for recurrent CDI at a single center between January 2012 and December 2016.[21] Median time from last FMT to follow-up was 22 months. Overall at follow-up, 82% (113/137) of patients had no recurrence of CDI (nonrecurrent CDI group) and 18% (24/137) of patients had CDI (recurrent CDI group). The survey results suggested that antibiotic exposure for non-CDI infections after FMT were more common in the recurrent CDI group (75%) than in the nonrecurrent CDI group (38%; $p<0.001$). Overall, 82% of patients reported being symptom-free.

In another retrospective study, Meighani et al (2017) assessed outcomes from FMT for recurrent CDI in patients with inflammatory bowel disease (IBD).[22] All patients underwent FMT between December 2012 and May 2014 within a single health care system. Demographic and clinical characteristics as well as treatment outcomes for patients with IBD were compared with those of the general population within this system. Of 201 patients who underwent FMT, 20 had concurrent IBD, and the study found that the response to FMT and CDI relapse rate in the IBD group (n=20) did not differ statistically from the rest of the cohort (n=201). The overall response rate in the IBD population was 75% at 12 weeks. Study design, lack of a standardized FMT treatment protocol, and variable donors limit certainty in conclusions drawn from these data.

Pediatric Populations

Tun et al (2022) performed a systematic review and meta-analysis to assess the efficacy of FMT for the treatment of CDI in children.[23,] The analysis included 904 children across 14 observational studies (5 prospective, 5 retrospective, and 4 case series); 12 studies included children with recurrent CDI and 2 studies included children with recurrent CDI or first episode of CDI. The most common route of FMT administration was colonoscopy (49.79%). The primary outcome was the efficacy of FMT in treating CDI or recurrent CDI. Results demonstrated a rate of success ranging between 66% and 100%, the latter of which was found in 7 studies. The pooled rate of clinical success in the overall cohort was 86% (95% CI, 77 to 95; p<.001). There were 47 adverse events in 45 patients and 38 serious adverse events in 36 patients; the causes of serious adverse events were variable and there was no single predominant cause.

Procedural Approaches

Route of Administration

Systematic Reviews

A systematic review and meta-analysis by Du et al (2021) evaluated the efficacy of FMT delivery via oral capsules for the treatment of recurrent CDI.[24] The analysis included 12 case series and 3 RCTs (N=763 patients). Encapsulated delivery of FMT demonstrated an overall efficacy rate of 82.1% (95% CI, 76.2 to 87.4). There was no statistically significant difference in the efficacy of FMT capsules that used lyophilized stool versus frozen stool (p=.37). There was also no statistically significant difference in the efficacy of FMT capsules compared with colonoscopy (RR, 1.01; 95% CI, 0.95 to 1.08). No serious adverse events attributable to oral FMT capsules were reported, other than those associated with treatment failure.

A systematic review and meta-analysis by Ramai et al (2020) compared several routes of FMT delivery for the treatment of recurrent CDI.[25] Twenty-six studies (N=1309) were included; colonoscopy was used in 16 studies (n=483), nasogastric/nasoduodenal tube in 5 studies (n=149), enema in 4 studies (n=360), and oral capsules in 4 studies (n=301). The pooled cure rates for colonoscopy, capsules, enema, and nasogastric/nasoduodenal tube were 94.8%, 92.1%, 87.2%, and 78.1%, respectively. Cure rates were significantly higher with colonoscopy versus nasogastric tube or enema (p<0.001 for both); capsules were also superior to nasogastric tube (p<0.001) and enema (p=0.005). The difference in cure rates did not reach statistical significance when comparing colonoscopy and capsules (p=0.126).

The review by Quraishi et al (2017), discussed previously, included a subgroup analysis of FMT delivery.[16] Pooled analysis of 7 RCTs and 25 case series revealed a significant difference between lower gastrointestinal delivery (95%; 95% CI, 92% to 97%) and upper gastrointestinal delivery (88%; 95% CI, 82% to 94%; p=0.02). Reviewers concluded that FMT appeared to be effective in the treatment of recurrent and refractory CDI, independent of the delivery route.

Randomized Controlled Trials

An RCT published by Youngster and colleagues in 2014, compared infusion of donor stools by colonoscopy or nasogastric tube.[26] Twenty patients with relapsing and recurrent CDI were included. Patients needed to have a relapse of CDI following at least 3 episodes of mild-to-moderate CDI and failure of a course of vancomycin or at least 2 episodes of severe CDI that resulted in hospitalization and was associated with significant morbidity. All patients underwent FMT and were randomized to 1 of 2 infusion routes, colonoscopy or a nasogastric tube. Both groups had 90cc-thawed inoculum. Stool donors were healthy non-relatives who successfully completed an extensive screening process. Stool was frozen up to 156 days before use. Patients could receive a second FMT if symptoms did not resolve following the initial transplant. The primary efficacy outcome was clinical cure, defined as resolution of diarrhea (i.e., <3 bowel movements per 24 hours) while off antibiotics for CDI, without relapse for 8 weeks. Fourteen patients were cured after the first FMT, 8 in the colonoscopy group and 6 in the nasogastric tube group; the difference between groups was not statistically significant (p=0.628). Of the remaining 6 patients, 1 refused additional treatment and the other 5 underwent a second transplant. According to the study protocol, patients could choose the route of administration for the second procedure and all of them chose the nasogastric tube. Four additional patients were cured after the second transplant, for an overall cure rate of 18 (90%) of 20. This study did not find that either route of administration of donor feces was superior to the other, but patients preferred use of a nasogastric tube.

Fresh Versus Frozen Feces

Systematic Reviews

Gangwani et al (2023) published a systematic review comparing fresh vs frozen vs lyophilized FMT for recurrent CDI.[27,] A total of 616 patients were included across 8 studies (4 RCT and 4 cohort); all 8 studies evaluated fresh FMT, 6 also assessed frozen FMT, and 3 assessed lyophilized FMT. Fresh FMT was determined to be most successful for the resolution of symptoms with 93% efficacy, followed by frozen at 88% efficacy and lyophilized at 83% efficacy. There were no significant differences in efficacy between frozen vs fresh FMT groups (risk difference, -0.051; 95% CI, -0.116 to 0.014; p=.178) or frozen vs lyophilized groups (risk difference, 0.061; 95% CI, -0.038 to 0.160).

The review by Ramai et al (2020), discussed previously, included a subgroup analysis of FMT preparation.[25] The overall cure rates were similar amongst patients treated with FMT that used fresh (n=556) versus frozen (n=753) stool (94.9% and 94.5%, respectively).

The 2017 Quraishi systematic review also included a subgroup analysis of FMT preparation.[16] Only 1 RCT in the review directly compared the effects of fresh stool to prepare FMT (n=11) with frozen stool to prepare FMT (n=108) on CDI resolution (RR=1.19; 95% CI, 0.77 to 1.84). The remaining 30 case series used frozen stool to prepare FMT. Two RCTs and 2 case series used fresh stool to prepare FMT. The pooled analyses found no difference between fresh FMT (92%;

95% CI, 89% to 95%), with moderate heterogeneity (I^2=54%) and frozen FMT (93%; 95% CI, 87% to 97%; p=0.84), with minimal heterogeneity reported (I^2=19%). Reviewers concluded that FMT appeared to be effective in the treatment of recurrent and refractory CDI, independent of FMT preparation.

Randomized Controlled Trials

A 2016 double-blind RCT by Lee et al compared fresh versus frozen stool used in FMT for patients with recurrent CDI.[28] A total of 232 patients were included, 114 assigned to frozen FMT and 118 to fresh FMT. The primary end point was the proportion of patients with no recurrence of CDI-related diarrhea 13 weeks after FMT. The study was designed as a noninferiority RCT and had a noninferiority margin of 15%. In the per protocol population (n=178), the rate of clinical resolution of symptoms was 76 (83.5%) of 91 in the frozen FMT group and 74 (85.1%) of 87 in the fresh FMT group (difference, -1.6%; 95% 1-sided CI, -10.5% to infinity). In the modified ITT group, the rate of clinical resolution with up to 2 FMTs was 81 (75.0%) of 108in the frozen FMT group and 78 (70.3%) of 111 in the fresh FMT group (difference, 4.7%; 95% 1-sided CI, -5.2% to infinity). The difference between groups was within the 15% noninferiority margin and thus frozen FMT was considered noninferior to fresh FMT.

Donor Versus Autologous Feces

Systematic reviews

The review by Ramai et al (2020) also included a subgroup analysis of donor relation.[25] Results demonstrated that cure rates were not significantly influenced by whether FMT used unrelated or a mix of related and unrelated donors (94.5% and 95.7%, respectively). The review by Rokkas et al (2019), discussed previously, included a subgroup analysis of donor relation.[9] Using data from a single RCT, results demonstrated the superiority of dFMT over aFMT for resolution of CDI symptoms (OR, 6.42; 95% CrI, 1.28 to 57.74). The wide CrI creates uncertainty regarding the difference between these interventions.

Long-term Outcomes

Lee et al (2019) performed a prospective study assessing the long-term durability and safety of FMT for patients with recurrent or refractory CDI.[29] Ninety-four patients underwent FMT via retention enema between 2008-2012; 32 patients were unreachable and 37 were deceased 4 to 8 years later for a follow-up survey. Twenty-three of the remaining 25 patients completed the questionnaire. No CDI recurrences were reported in patients treated with FMT. 12 of 23 participants (52.2%) received at least 1 course of antibiotics for treatment of a condition other than CDI. Nine participants (40.9%) received probiotics. Current health was self-reported as "much better" in 17 patients (73.9%) or "somewhat better" in 3 patients (13.0%). The authors concluded that FMT for recurrent or refractory CDI appears to be durable at 4-8 years following treatment, even after receiving non-CDI antibiotic therapy.

Fecal Microbiota Transplantation (FDA-approved products)

Clinical Context and Therapy Purpose

The purpose of FMT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with recurrent CDI refractory to antibiotic therapy.

The following **PICO** was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with recurrent CDI refractory to antibiotic therapy.

Interventions
The therapy being considered is commercially available, FDA-approved FMT products: rectally administered live fecal microbiota spores (Rebyota) and orally administered live fecal microbiota spores (Vowst).

Comparators
The following therapy is currently being used to treat CDI: standard antibiotic regimens.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Follow-up ranging up to and beyond 12 weeks is of interest to monitor for outcomes. Outcomes reported in FMT trials for CDI include clinical cure, resolution of CDI with no further recurrence, or reduced risk of CDI recurrence. There are inconsistencies across these trials in how CDI resolution (i.e., treatment success) and recurrence are defined and measured.[8,9,] Treatment success generally required a resolution of diarrhea symptoms with or without laboratory confirmation. Up to 3 consecutive negative stool tests for *C. difficile* toxin have been required to define cure in one trial. Conversely, recurrence generally required the presence of diarrhea with or without laboratory confirmation or the need for further treatment for up to 17 weeks after the incident case. The 2017 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America guideline for CDI recommends against repeat testing for *C.difficile* toxin during the same episode of diarrhea or for asymptomatic patients, since >60% of patients may remain positive for the *C. difficile* toxin even after successful treatment.[10,]Per the 2017 IDSA/SHEA guideline, a recurrent case occurs within 2 to 8 weeks of the incident case and requires both clinical plus laboratory evidence of disease for diagnosis. The 2021 update to the IDSA/SHEA guideline does not comment on repeat testing nor does it provide an updated definition of recurrent CDI.[11,] Per 2 separate 2021 guidelines from the American Society of Colon and Rectal Surgeons (ASCRS) and American College of Gastroenterology (ACG), a recurrent case occurs within 8 weeks after the completion of a course of CDI therapy and requires both clinical plus laboratory evidence of disease for diagnosis.[12,13,]

Randomized Controlled Trials
Summaries of clinical trials investigating commercially available, FDA-approved FMT therapies and their respective results are provided in Tables 2 and 3, respectively.

The FDA approval of rectally administered live fecal microbiota spores was based on a phase 3 double-blind, placebo-controlled RCT (PUNCH CD3; n=289), with analysis conducted using a Bayesian hierarchical model that borrowed data from a preceding phase 2b trial (PUNCH CD2; n=134).[30,31,] This approach was chosen due to the widespread availability and utilization of FMT, which posed challenges for enrolling patients into a placebo-controlled trial. Both trials enrolled adults with recurrent CDI (1 or more recurrences in PUNCH CD3, and 2 or more recurrences in PUNCH CD2) or a minimum of 2 CDI episodes within the preceding year that led to hospitalization. Enrolled patients received at least 10 consecutive days of standard antibiotic therapy and displayed improvement in CDI symptoms. In PUNCH CD3, patients were randomized 2:1 to receive a single dose of rectally administered live fecal microbiota spores or placebo following a 24- to 72-hour washout period after standard-of-care antibiotic therapy. In PUNCH CD2, patients were randomized 1:1:1 to receive either 2 doses of rectally administered live fecal

microbiota spores, 2 doses of placebo, or 1 dose of each, administered approximately 1 week apart, also following a 24- to 72-hour washout period after standard-of-care antibiotic therapy. Importantly, in the Bayesian analysis, the model only incorporated data from the 1-dose active treatment group and the placebo control group of the PUNCH CD2 study (not the 2-dose active treatment group). Treatment success, defined as the absence of CDI within 8 weeks of study treatment, was the primary outcome of the trials. Initial predictions from the model indicated treatment success rates of 70.4% for active treatment and 58.1% for placebo. However, after aligning the data to improve the exchangeability and interpretability of the Bayesian analysis, the model-calculated treatment success rates for active and placebo treatment were 70.6% and 57.5%, respectively. These adjustments resulted in an estimated treatment effect of 13.1% (95% CI, 2.3 to 24.0) and a posterior probability of superiority at 0.991 in favor of rectally administered live fecal microbiota spores. Additionally, among those patients who achieved treatment success at 8 weeks, more than 90% remained free of CDI recurrence through 6 months. The incidence of adverse events was similar between treatment groups and most were mild-to-moderate in severity.

The FDA approval of orally administered live fecal microbiota spores was based on the ECOSPOR III trial.[32.] In this trial, 182 adults with at least 3 episodes of CDI in the previous 12 months (i.e., 2 or more recurrences within 12 months) who received 10 to 21 consecutive days of standard antibacterial therapy with improvement in CDI symptoms were randomized to receive 4 orally administered capsules containing live fecal microbiota spores or placebo once daily for 3 consecutive days. The trial demonstrated that the recurrence rate of CDI was significantly lower with orally administered live fecal microbiota spores compared to placebo at up to 8 weeks after treatment (12% vs 40%; RR, 0.32; 95% CI, 0.18 to 0.58). In a subsequent publication evaluating the durability of response, the rate of CDI recurrence after 24 weeks of follow-up was 21.3% following orally administered live fecal microbiota spores and 47.3% following placebo (RR, 0.46; 95% CI, 0.30 to 0.73); the median (range) time to recurrence was 3.3 (0.6 to 23.4) weeks and 1.6 (0.6 to 18.1) weeks, respectively.[33.] The incidence of adverse events was similar between treatment groups and most were mild-to-moderate in severity.

Table 2. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Khanna (2022); PUNCH CD3	US, Canada	44	2017-2020	Adults with ≥2 episodes of CDI within 12 months or ≥2 episodes of severe CDI requiring hospitalization; completed ≥10 days of SOC antibiotic therapy.	Following a 24 to 72-hour wash-out period after SOC antibiotic treatment for CDI, one dose of rectally administered live fecal microbiota spore suspension (n=193)	Normal saline (n=96)
Feuerstadt (2022); ECOSPOR III	US, Canada	56	2017-2020	Adults with ≥3 episodes of CDI within 12 months, inclusive of the qualifying acute episode; resolution of symptoms while receiving 10 to 21 days of SOC antibiotic therapy.	Orally administered live fecal microbiota spores(approximately 3×10^7 spore colony-forming units)via 4 capsules once daily for 3 consecutive days (n=89)	Matching placebo capsules (n=93)

CDI: *Clostridioides difficile* infection; RCT: randomized controlled trial; SOC: standard of care.

Table 3. Summary of Key RCT Results

Study	Treatment failure: CDI recurrence ≤8 weeks after treatment	Treatment success: no CDI recurrence ≤8 weeks after treatment	Adverse events	Serious adverse events
Khanna (2022); PUNCH CD3		N=289	N=267	N=267
Rectally administered live fecal microbiota spores		70.6%	55.6%	3.9%
Placebo		57.5%	44.8%	2.3%
Treatment effect (95% CI)[a]		13.1% (2.3 to 24.0)	NR	NR
Posterior probability		.99136		
Feuerstadt (2022)·; ECOSPOR III	N=182		N=182	N=182
Orally administered live fecal microbiota spores	12%		93%	16%
Placebo	40%		91%	8%
RR (95% CI)	0.32 (0.18 to 0.58)		NR	NR

CI: confidence interval; CDI: *Clostridioides difficile* infection; NR, not reported; RCT: randomized controlled trial; RR: relative risk.
[a]PUNCH CD3 was analyzed using a Bayesian hierarchical model borrowing data from the previous phase 2b trial (PUNCH CD2). The model incorporated data from the PUNCH CD2 study from the 1-dose active treatment group and placebo control group (not the 2-dose active treatment group).

The purpose of the study limitations tables (see Tables 4 and 5) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Khanna (2022)·; PUNCH CD3	3. Authors reported that approximately one-third of PUNCH CD3 participants were enrolled after only 1 CDI recurrence. 4. >90% White participants enrolled 5. Study excluded participants with irritable bowel syndrome and inflammatory bowel disease, and those who were immunocompromised				

OFeuerstadt (2022)[,]; ECOSPOR III	4. >90% White participants enrolled 5. Study excluded participants with irritable bowel syndrome and inflammatory bowel disease, and those who were immunocompromised				1,2. Only 16-week follow up

CDI: *Clostridioides difficile* infection.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Khanna (2022)[,]; PUNCH CD3						
Feuerstadt (2022)[,]; ECOSPOR III	5. Enrollment truncated due to COVID-19 pandemic					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Observational studies

Sim et al (2023) published a phase 3, single-arm, open-label, 24-week study (ECOSPOR IV) that evaluated the safety and rate of CDI recurrence after oral administration of capsules containing live fecal microbiota spores.[34,] The trial included adults with recurrent CDI who were enrolled in one of 2 cohorts: 1) rollover patients from the ECOSPOR III trial who had CDI recurrence diagnosed by toxin enzyme immunoassay; 2) patients with at least 1 CDI recurrence, inclusive of their acute infection at study entry. Participants received 4 capsules containing active treatment or placebo orally once daily for 3 consecutive days, following standard antibacterial therapy with improvement in CDI symptoms. A total of 263 patients were enrolled; 29 in cohort 1 and 234 in cohort 2. Seventy-seven patients (29.3%) were enrolled with their first CDI recurrence. Overall, 141 patients (53.6%) had treatment-emergent adverse effects, which were mostly mild to

moderate and gastrointestinal. Recurrent CDI at week 8 was identified in 23 patients (8.7%) (4 of 29 [13.8%] in cohort 1 and 19 of 234 [8.1%] in cohort 2), and recurrent CDI rates remained low through 24 weeks (36 patients [13.7%]).

Section Summary: Recurrent *Clostridioides difficile* Infection
For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT with a product that is not commercially available, the evidence includes systematic reviews with meta-analyses and observational studies. Meta-analyses have found that FMT is more effective than standard treatment or placebo for patients with recurrent CDI. A long-term prospective study found that FMT for recurrent or refractory CDI appears to be durable at 4 to 8 years following treatment, even for patients who had subsequently received non-CDI antibiotic therapy. A meta-analysis comparing several routes of FMT delivery for the treatment of recurrent CDI found that cure rates were significantly higher with colonoscopy or oral capsules versus nasogastric tube or enema, while colonoscopy and capsules were equally effective. Similar success rates have been demonstrated with FMT using fresh versus frozen feces. Conversely, data regarding the superiority of FMT using donor versus autologous feces are conflicting. Few treatment-related adverse events have been reported.

For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT with an FDA-approved product, the evidence includes RCTs and an observational study. The efficacy of a commercially available rectally administered suspension containing live fecal microbiota spores was evaluated in a phase 3 double-blind, placebo-controlled RCT (PUNCH CD3; N=289), with analysis conducted using a Bayesian hierarchical model that borrowed data from a preceding phase 2b trial (PUNCH CD2; N=134). Both trials included adults with recurrent CDI (1 or more recurrences in PUNCH CD3, and 2 or more recurrences in PUNCH CD2) or a minimum of 2 CDI episodes within the preceding year that led to hospitalization, who received at least 10 consecutive days of standard antibiotic therapy and displayed improvement in CDI symptoms. The rate of treatment success, defined as the absence of CDI within 8 weeks of study treatment, was significantly higher in the group of patients who received rectally administered live fecal microbiota spores as compared to placebo (70.6% vs 57.5%). Additionally, among those patients who achieved treatment success at 8 weeks, more than 90% remained free of CDI recurrence through 6 months. A phase 3, double-blind, placebo-controlled RCT (N=182) evaluated the efficacy of commercially available oral capsules containing live fecal microbiota spores in patients who had at least 2 recurrences within 12 months and who received 10 to 21 consecutive days of standard antibiotic therapy and displayed improvement in CDI symptoms. Results demonstrated that a 3-day course of oral live fecal microbiota spores was more effective than placebo at preventing CDI recurrence within 8 weeks of treatment (12% vs 40%, respectively). In a single-arm, open-label trial evaluating commercially available oral capsules containing live fecal microbiota spores, the CDI recurrence rate at 24 weeks follow-up was 13.7%. Both commercially available therapies were well-tolerated, with the majority of adverse events being mild-to-moderate in severity.

INFLAMMATORY BOWEL DISEASE

Clinical Context and Therapy Purpose
The purpose of FMT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with IBD.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with IBD. Individuals with IBD include subsets of patients with ulcerative colitis (UC) and Crohn disease (CD).

Interventions
The therapy being considered is FMT. Patients with IBD are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Comparators
The following therapy is currently being used to treat IBD: standard of care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. In clinical trials of FMT for CD or UC, there are inconsistencies in reported outcomes. Clinical remission was the most commonly reported outcome, but study definitions varied.

According to the 2019 American Gastroenterological Association guidelines for moderate to severe UC, the following outcomes should be used for decision-making for adults with moderate to severe UC:[25]

- Induction and maintenance of remission
- Short-term colectomy risk (within 3 months of hospitalization)

Other important outcomes recognized by these guidelines include:

- Induction and maintenance of endoscopic remission
- Maintenance of corticosteroid-free remission
- Serious adverse events (including serious infections and malignancy)
- Treatment tolerability (drug discontinuation due to adverse events)

According to the 2018 American Gastroenterological Association guidelines for CD, common outcomes in clinical trials of CD patients include measurements of Crohn's disease activity index (CDAI), the Harvey Bradshaw Index, and other patient-reported outcome tools.[28] With regard to remission, the guidelines stress that patients with CD may be in histologic, endoscopic, clinical, or surgical remission. The guidelines note there has been a recent push to more patient-reported outcomes and objective measures of disease (endoscopy findings) versus CDAI. Mucosal healing is an important target in assessing the efficacy of therapies for IBD. In this population, mucosal healing is defined as an absence of ulceration. Endoscopic scoring systems have been developed to quantify the degree of ulceration and inflammation in patients with CD. The Simple Endoscopic Score for Crohn's disease (SES-CD) has been used to assess endoscopic activity in clinical practice.

The 2021 AGA guideline for moderate to severe luminal and perianal fistulizing CD recognizes the following outcomes of interest for decision-making in this arena:[29,]

- Induction and maintenance of endoscopic remission
- Maintenance of corticosteroid-free remission
- Serious adverse events (including serious infections and malignancy)
- Treatment tolerability (drug discontinuation due to adverse events).

Systematic Reviews

A 2023 Cochrane review by Imdad et al. included 12 studies (N=550) that evaluated the efficacy and safety of FMT for the treatment of IBD.[38] The follow-up duration across studies ranged from 6 to 12 weeks for the evaluation of induction and from 48 to 56 weeks for the evaluation of remission. Comparators included autologous FMT, placebo, standard medication, and no intervention. FMT was administered in the form of capsules or suspensions for oral administration, nasoduodenal tube, enema, or colonoscopy. The results demonstrated that FMT significantly increased the likelihood of induction of clinical remission in UC compared to the control (risk ratio, 1.79; 95% CI, 1.13 to 2.84). However, FMT did not significantly improve the likelihood of induction of endoscopic remission. Furthermore, FMT did not significantly improve the maintenance of clinical or endoscopic remission of UC. There were no statistically significant differences in the rates of adverse events or serious adverse events.

Tan et al (2022) performed a systematic review and meta-analysis evaluating 14 RCTs of FMT for the treatment of patients with IBD.[39] The included studies involved a total of 666 patients with UC (n=12 studies) and CD (n=2 studies). The control groups in the RCTs utilized varying interventions including placebo, sham procedures, isotonic saline, a special UC diet, and conventional treatment. Clinical remission of IBD was reported in 11 studies and FMT had a significant effect as compared to placebo (RR, 1.44; 95% CI, 1.03 to 2.02; p=.03), with no significant risk of study heterogeneity. Clinical response was reported in 8 studies and FMT led to improved results as compared to placebo (RR, 1.34; 95% CI, 0.92 to 1.94; p=.12), with moderate between-study heterogeneity. Subgroup analysis revealed increased clinical remission with fresh versus frozen FMT (40.9% vs. 32.2%). Most adverse events of therapy were mild and self-limiting. Limitations of this review included variations in FMT infusion frequencies, number of donors, and preparation and storage of donor stools. Additionally, subgroup analyses were limited by the small number of studies and insufficient sample size.

Fehily et al (2021) conducted a systematic review evaluating the efficacy of FMT in CD.[40] The review included 15 studies: 2 RCTs and 13 prospective cohort studies. Ten studies included patients with CD only and the remaining 5 studies included other IBD subtypes, with separated results. Of note, 6 publications examined data from the same clinical trial; only the most recently published study with the largest dataset was included. Therefore, 10 studies were analyzed with a total of 293 patients. The majority of studies evaluated FMT for induction of remission, with follow-up duration ranging from 4 to 52 weeks. Six studies reported treatment with a single FMT treatment while the remaining 4 studies administered FMT repeatedly (2 to 8 treatments) across a wide time interval of 1 day to 6 months. Results revealed that the clinical response rates in early follow-up were increased with multiple FMT as compared to a single FMT; FMT dose and use of fresh or frozen FMT did not influence clinical outcomes. There was an increase in early efficacy rates with FMT delivered via the upper gastrointestinal route (75% to 100%) as compared with lower delivery routes (30% to 58%); however, this difference was not maintained after 8 weeks. No serious adverse events were observed with FMT therapy. Limitations of this review included the small number of studies with widely varying study designs and that not all studies utilized standardized validated clinical indices for assessing clinical response and remission.

A systematic review and meta-analysis by Zhou et al (2020) searched for studies to September 2019 evaluating the efficacy and safety of FMT, biological agents, and tofacitinib in patients with UC.[41] Sixteen RCTs were identified (4 with FMT, 10 with biological agents, and 2 with tofacitinib). Compared with the placebo, the clinical response was significantly higher with FMT (RR, 1.648;

95% CI, 1.253 to 2.034) as was clinical remission (RR, 2.486; 95% CI, 1.393 to 4.264). Indirect comparisons did not reveal any statistically significant differences between FMT and adalimumab, infliximab, golimumab, vedolizumab, or tofacitinib for either clinical response or clinical remission. The incidence of adverse events was also similar when comparing FMT to biologics or tofacitinib.

A systematic review and meta-analysis by Paramsothy et al (2017) searched for studies to January 2017 evaluating the efficacy and/or safety of FMT use in treating IBD, distributed across 3 disease subtypes (ulcerative colitis [UC], Crohn disease [CD], pouchitis).[42] Fifty-three studies were selected and analyzed for this review (41 in UC, 11 in CD, 4 in pouchitis). Overall, 36% (201/555) of UC patients, 50.5% (42/83) of CD patients, and 21.5% (5/23) of pouchitis patients achieved the primary outcome of clinical remission. Pooled proportion achieving clinical remission was 33% among cohort studies, with a moderate risk of heterogeneity; among the 4 RCTs selected, there was a significant benefit in clinical remission (odds ratio, 2.89; 95% CI, 1.36 to 6.13; p=0.006), with moderate heterogeneity. Transient gastrointestinal complaints comprised most of the adverse events. Reviewers concluded that FMT appeared most promising in treating UC, and use of FMT to treat CD should be interpreted cautiously, due to wide confidence intervals.

Randomized Controlled Trials

Along with the summaries below, Tables 6 and 7 provide an overview of the characteristics and results of selected RCTs. Tables 8 and 9 summarize the study relevance, design, and conduct limitations.

Lahtinen et al (2023) published results of a small (N=48) RCT in Finland investigating FMT for the maintenance of remission in patients with UC.[43.] To be included in the trial, patients with UC had to be in remission, have fecal calprotectin levels below 100 µg/g, and have a clinical Mayo score of less than 3 at the time of screening. The exclusion criteria included the use of antibiotics within 3 months prior to study entry, a history of biologic use, and the use of high doses of corticosteroids. Patients were randomized 1:1 to receive a single-dose FMT or autologous (i.e., control) transplant via colonoscopy. The primary endpoint was sustained remission through the 12-month follow-up, defined as a fecal calprotectin level below 200 µg/g and a clinical Mayo score below 3. At baseline, the majority of the patients were on mesalazine. Results demonstrated that the rate of achievement of the primary endpoint did not differ between FMT and control groups (54% vs 41%; p=.660); however, the trial was potentially underpowered as the sample size calculation called for 40 patients in each group. Overall, FMT was well tolerated with no serious adverse events reported.

Crothers et al (2021) published results of a small, single-center, placebo-controlled RCT in the US investigating long-term encapsulated delivery of FMT in patients with mild to moderate UC.[44.] Patients in the FMT group received induction FMT via colonoscopy, followed by 12 weeks of oral maintenance therapy with frozen FMT capsules. Patients were required to be on stable doses of UC-specific medications for at least 6 weeks prior to screening, including tumor necrosis factor inhibitors, oral immunomodulators, oral and topical 5-aminosalicylates, and methotrexate; corticosteroid use was not allowed. Patients in both study groups were pretreated with ciprofloxacin and metronidazole for 7 days prior to randomization to FMT or placebo. No primary outcome was identified; clinical remission (defined as a modified Mayo score ≤2 at 12 weeks plus achievement of several prespecified subscores) and clinical response (defined as a decrease in total Mayo score ≥3 points at 12 weeks plus achievement of several prespecified subscores) were measured. Due to difficulties recruiting patients who met inclusion/exclusion criteria, enrollment

was terminated early when only 15 of the expected 20 patients were enrolled; furthermore, 1 patient in the FMT group and 2 in the placebo group did not meet endoscopic criteria for inclusion and were excluded from the study after randomization. The only serious adverse event was a worsening of disease activity, which occurred in 1 patient in each group.

Fang et al (2021) published results of a small, single-center, open-label RCT in China investigating monotherapy with FMT for recurrent UC.[45.] Patients in the FMT group received a single instillation of FMT via colonoscopy; the control group received standard of care UC treatments. Enrolled patients were previously treated with 5-aminosalicylates at stable doses for at least 4 weeks, but had received no other therapy, including immunosuppressive agents or biologics. The primary outcome was steroid-free remission of UC (defined as a total Mayo score ≤2 with an endoscopic Mayo score of ≤1). Patients were followed for up to 24 months after treatment. Overall, FMT was well tolerated with no serious adverse events reported.

Sokol et al (2020) published the results of a small, multicenter, single-blind, placebo-controlled RCT in France investigating endoscopic delivery of FMT in patients with CD.[46] Patients could not be on concomitant tumor necrosis factor inhibitors, and those with active disease at screening were treated with oral prednisone. Only those patients who achieved clinical remission within the 3 weeks following the commencement of corticosteroids (defined as a Harvey Bradshaw Index <5) were randomized to treatment or placebo. The treatment group received FMT after colon cleansing with polyethylene glycol. The primary endpoint was the colonization of donor microbiota at week 6. Colonization was defined as being successful if the fecal microbiota of the recipient 6 weeks after FMT was more similar to the fecal microbiota of the donor than to the recipient before FMT; similarity was assessed using Sorensen's index, and a score ≥0.6 signaled successful colonization. The rate of clinical flares in the 24 weeks following FMT was a secondary endpoint in the study. A clinical flare was defined as any 1 of the following: a CDAI > 220 points, a CDAI between 150 and 220 with an increase >70 compared with baseline, the need for surgery, or the need to start a new medical treatment for CD. Eight patients received FMT and 9 received placebo treatment. None of the adverse events observed in the trial were considered to be related to FMT.

Sood et al (2019) published results of a 48-week small single-center RCT in India evaluating maintenance FMT (n=31) versus placebo (n=30) in patients with UC receiving standard of care therapies who are in clinical remission after prior FMT sessions.[47] The primary endpoint was the maintenance of steroid-free clinical remission (Mayo score ≤2 and all subscores ≤1) at week 48. Relapse occurred in 3 patients in the FMT group and 8 patients in the placebo group. There were no serious adverse events reported in this trial.

Table 6. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Lahtinen et al (2023)	Finland	NR	2014-2020	Patients with UC in remission (fecal calprotectin <100 µg/g; Mayo score <3)	n=24; initial FMT via colonoscopy (250 mL at a concentraion of 10%)	n=24; sham colonoscopic infusion of autologous fecal suspension using participant's own stool
Crothers et al (2021)	US	1	2016-2017	Patients with UC (Mayo score 4-	n=7; initial FMT via colonoscopy (120 mL at	n=8; sham colonoscopic infusion

				10) with inflammation extending proximally to at least the recto-sigmoid junction	a concentration of 1 g of stool/2.5 mL) followed by 12 weeks of oral maintenance therapy with frozen FMT capsules (0.5 g of stool/capsule)	and sham capsules visually resembling fecal material
Fang (2021)	China	1	2017-NR	Patients with recurrent active UC (Mayo score 4-10)	n=10; single fresh FMT via colonoscopy (200 mL of donor fecal slurry delivered into the right and left colon)	n=10; standard of care (patients with mild to moderate UC were treated with mesalazine, and patients with severe UC were treated with corticosteroids for induction therapy and mesalazine for maintenance therapy)
Sokal et al (2020)	France	6	2014 to 2017	CD with colonic or ileocolonic involvement; patients with active disease at screening were treated with oral prednisone	n=8; FMT using 50 to 100 g of fresh donor stool resuspended in 250 to 350 ml of sterile sodium chloride, filtered, and administered in the cecum during colonoscopy	n=9; vehicle physiological serum administered in the cecum during colonoscopy
Sood et al (2019)	India	1	2015 to 2017	Patients with UC in clinical remission (Mayo score ≤2 and each subscore of ≤1) after prior FMTs	n=31; FMT using 100 g of fresh donor stool resuspended in 200 ml of sterile sodium chloride, filtered, and administered via retention enema (4 to 6 hours) every 8 weeks; standard of care UC therapies were allowed	n=30; preservative-free normal saline with food-grade color via retention enema (4 to 6 hours) every 8 weeks; standard of care UC therapies were allowed

CDI: *Clostridioides difficile* infection; FMT: fecal microbiota transplantation; NL: Netherlands; NR: not reported; UC: ulcerative colitis.

Table 7. Summary of Key Randomized Trial Results

Study	**Outcome, n (%)**	
	Active	**Comparator**
Lahtinen et al (2023)	n=24 (FMT)	n=24 (autologous FMT)
Maintenance of remission at 12 months[1]	13 (54)	10 (41)
p-value	0.660	
Crothers et al (2021)	N=6 (FMT)	N=6 (placebo)
Clinical remission at 12 weeks[1]	2 (33)	0 (0)
p-value	.45	
Clinical response at 12 weeks[1]	3 (50)	1 (17)

p-value	.55	
Fang (2021)	N=10 (FMT)	N=10 (standard of care)
Steroid-free remission at 8 weeks[2]	9 (90)	5 (50)
p-value	NR	
Sokol et al (2020)	N=8 (dFMT)	N=9 (placebo)
Successful colonization[3]	0	0
Flare-free survival at week 24[3]	5 (62.5)	3 (33.3)
p-value	.23	
Steroid-free clinical remission at Week 103	7 (87.5)	4 (44)
p-value	.13	
Sood et al (2019)	N=31 (dFMT)	N=30 (placebo)
Steroid-free clinical remission at week 48[4]	21 (87.1)	20 (66.7)
p-value	.111	
Endoscopic remission at week 48[4]	18 (58.1)	8 (26.7)
p-value	.026	
Histological remission at week 48[4]	14 (45.2)	5 (16.7)
p-value	.033	

dFMT: donor fecal microbiota transplantation
[1]Colonization was defined as being successful if the fecal microbiota of the recipient 6 weeks after FMT was more similar to the fecal microbiota of the donor than to the recipient before FMT; similarity was assessed using Sorensen's index, and a score ≥0.6 signaled successful colonization.
[2]A clinical flare was defined as any one of the following: a CDAI > 220 points, a CDAI between 150 and 220 with an increase >70 compared with baseline, the need for surgery, or the need to start a new medical treatment for CD.
[3] Steroid-free clinical remission was not explicitly defined by authors.
[4] Steroid-free clinical remission was defined as Mayo score ≤2 and sub scores ≤1
[5] Endoscopic remission was defined as Mayo score 0
[6] Histological remission was defined as Nancy grade 0 or 1

Table 8. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Lahtinen et al (2023)	3. Unclear whether excluding patients who received certain standard of care therapies is appropriate or matches the intended use profile				
Crothers et al (2021)	4. Unclear whether excluding patients with severe disease is appropriate or matches the intended use profile			5. Clinically significant difference not prespecified	2. Not sufficient duration for harms
Fang (2021)	4. Unclear whether excluding patients with comorbidities is appropriate or matches the intended use profile			3. No CONSORT reporting of harms 5. Clinically significant difference not prespecified	
Sokol et al (2020)	4. Unclear whether excluding patients with severe disease is appropriate or matches the intended use profile		1. Type and quantity of vehicle used for the placebo group were not clearly defined	6. Rationale for Clinical significant difference not provided	2. Not sufficient duration for harms
Sood et al (2019)	4. Unclear whether excluding patients who received certain standard of care therapies is appropriate or matches the intended use profile				

FMT: fecal microbiota transplantation; UC: ulcerative colitis.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 9. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Lahtinen et al (2023)		1, 2. Investigators were not blinded to treatment			4. Power not reached for the primary outcome	
Crothers et al (2021)					2. Power not calculated for primary outcome	
Fang et al (2021)		1, 2. investigators and patients were not blinded to treatment	2. Evidence of selective reporting (not all prespecified outcome results were reported)		2. Power not calculated for primary outcome	
Sokol et al (2020)[30]		1, 2. investigators were not blinded to treatment				
Sood et al (2019)[31]					3. Power not reached for the primary outcome	

FMT: fecal microbiota transplantation; NCT: national clinical trial.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. No intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Long-term Outcomes

Li et al (2020) published the results of a prospective observational cohort study that included 202 patients with UC who underwent the first course of FMT at a single center in China between November 2012 to September 2018.[48] Patients with mild, moderate, and severe

active UC (Mayo score from 3 to 12) were included. Of the initial 202 patients, 122 patients who achieved clinical response at 1 month after the first course of FMT were included in the analysis for time of maintaining efficacy. Among these 122 patients, 22 patients had a sustained response without undergoing a second course of FMT until January 1, 2019 (the terminal point of follow-up), 77 patients had disease relapse before the second course of FMT, and 23 patients underwent consolidation therapy with a second course of FMT before disease relapse. The median follow-up was 25.5 months (interquartile range [IQR], 11.75 to 43 months). The median time of maintaining efficacy from the first course of FMT in 99 patients was 120 days (IQR, 45 to 180 days) and the median time of maintaining efficacy from the second course (i.e., consolidation) of FMT in 23 patients was 415 days (IQR, 255 to 780 days; p<0.001). No new safety issues were reported in this study.

The study by Sood et al (2019), discussed previously, reported results of a 48-week RCT evaluating maintenance FMT (n=31) versus placebo (n=30) in patients with UC receiving standard of care therapies who are in clinical remission after prior FMT sessions.[47] Maintenance of steroid-free clinical remission (Mayo score ≤2 and all subscores ≤1) was numerically higher in patients allocated to FMT (27 patients [87.1%]) versus placebo (20 patients [66.7%]), but the difference did not reach statistical significance (p=0.111). A significantly higher number of patients with FMT versus placebo achieved endoscopic remission (58.1% versus 26.7%; p=0.026) and histological remission (45.2% versus 16.7%; p=0.033). Three patients receiving FMT (9.7%) and 8 patients on placebo (26.7%) relapsed.

The study by Fang et al (2021), discussed previously, reported on long-term remission in patients with recurrent active UC who received either a single administration of FMT (n=10) or standard of care UC treatments (n=10).[45] The median remission time was 24 months in both the FMT (range, 6 to 38 months) and control (range, 7 to 35 months) groups (p=.895). No adverse events occurred during long-term follow-up.

Section summary: Inflammatory Bowel Disease
For individuals who have IBD who receive FMT, the evidence includes systematic reviews and RCTs. Systematic reviews have generally shown favorable clinical remission and response with FMT in patients with IBD while acknowledging that further RCTs and long-term follow-ups are needed to assess long-term effectiveness and safety. Additionally, a Cochrane review found that FMT did not significantly improve the maintenance of clinical or endoscopic remission of UC. A 48-week RCT in patients with UC in clinical remission after prior FMTs found conflicting results for remission outcomes with additional courses of FMT. Another RCT in patients with recurrent active UC found a median remission time of 24 months in both FMT and standard of care treatment groups. A 12-month RCT evaluating FMT for the maintenance of remission in patients with UC did not find a statistically significant difference between single-dose FMT and control groups. This current evidence is not sufficient to permit conclusions on the efficacy of FMT for UC. Additionally, questions remain about the optimal route of administration, donor characteristics, and the number of transplants. A small RCT in patients with CD failed to find a difference in the achievement of remission with FMT versus placebo.

IRRITABLE BOWEL SYNDROME

Clinical Context and Therapy Purpose
The purpose of FMT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with irritable bowel syndrome (IBS).

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant populations of interest are individuals with IBS. IBS is a gastrointestinal disordered marked by chronic abdominal pain with or without altered bowel movement patterns, in the absence of underlying damage or an identified cause. It is the most commonly diagnosed gastrointestinal condition, accounting for approximately 30% of all gastroenterologist referrals. The clinical prevalence as estimated from population-based studies in North America is approximately 10-15%. While the pathophysiology of IBS remains uncertain, the complex ecology of the fecal microbiota has led to speculation whether alterations in its composition could be associated with IBS.

Interventions
The therapy being considered is FMT. Patients with IBS are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Comparators
The following therapy is currently being used to treat IBD: standard of care. Standard of care may include lifestyle and dietary modifications, the establishment of a physical exercise program, and counseling to manage psychosocial factors. For patients with moderate to severe symptoms that impair quality of life, medication management with various symptom-targeting supplements and/or pharmacologic agents (e.g., soluble fiber, polyethylene glycol, osmotic laxatives, lubiprostone, linaclotide, tegaserod, loperamide, cholestyramine, and others) may be considered. For patients with refractory symptoms despite adjunctive pharmacologic therapy, food allergy testing, behavior modification, and pharmacological management of psychiatric impairment may be considered.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Though not completely standardized, follow-up for IBS would typically occur in the months to years after starting treatment.

Due to the absence of a biologic disease marker, IBS is often difficult to diagnose in the clinical setting. Several symptoms-based criteria have been developed in an effort to standardize the diagnosis of IBS. The most widely used criteria are the Rome IV criteria, which define IBS as recurrent abdominal pain, on average, at least one day per week in the last three months, associated with two or more of the following criteria[49]:

- Related to defecation, with an increase or improvement in pain
- Associated with a change in stool frequency
- Associated with a change in stool form (appearance)

The previous Rome III diagnostic criteria are less restrictive,[50] and are commonly featured in current studies on IBS. The Rome III criteria define IBS as recurrent abdominal pain or discomfort, 3 days per month in the last 3 months (12 weeks), associated with 2 or more of the criteria below:

- Improvement with defecation
- Onset associated with a change in stool frequency
- Onset associated with a change in stool form (appearance)

The Rome III criteria are fulfilled when symptoms have an onset six months prior to diagnosis.

Subtypes of IBS are based on patient-reported predominant bowel patterns on days with abnormal bowel movements and may utilize the Bristol stool form scale to record stool form and appearance. IBS subtypes defined for clinical practice include:

- IBS with predominant constipation (IBS-C): abnormal bowel movements with predominant constipation (type 1 and 2 on the Bristol stool form scale)
- IBS with predominant diarrhea (IBS-D): abnormal bowel movements with predominant diarrhea (type 6 and 7 on the Bristol stool form scale)
- IBS with mixed bowel habits (IBS-M): >1/4 of abnormal bowel movements constipation and >1/4 of abnormal bowel movements were diarrhea
- IBS unclassified: patients meet diagnostic criteria for IBS but cannot accurately be categorized into one of the three main subtypes

The Manning criteria is another diagnostic algorithm that may be used in the diagnosis of IBS, consisting of a questionnaire delivered to the patient by the treating clinician to establish the presence of typical symptoms. Positive diagnosis requires that three or more of the following symptoms are met:

- Pain relieved with defecation
- More frequent stools at the onset of pain
- Looser stools at the onset of pain
- Visible abdominal distention
- Passage of mucus
- Sensation of incomplete evacuation

A validation study comparing the Manning criteria to a previous version of the Rome criteria found it to have less sensitivity but greater specificity in diagnosing IBS.[4]

Measuring outcomes and severity of illness for patients in IBS can be challenging. The Rome Founding Working Team Report indicates that calculating severity in IBS is a complex matter, and is primarily determined by patient-reported symptoms, behaviors, and personal experience of illness. Severity must be understood through a broad integration of health-related quality of life, psychosocial factors, healthcare utilization behaviors, and burden of illness. Individual symptoms such as abdominal pain were considered important but insufficient determinants of IBS severity. Two validated severity measurement scales include the Functional Bowel Disorder Severity Index and the IBS Severity Scoring System (IBS-SSS). The Functional Bowel Disorder Severity Index assesses severity based on patient pain behaviors such as the presence and intensity of pain and the number of illness-related healthcare visits. Resultant scores categorize patients with mild (≤36), moderate (37-110) or severe (>110) IBS. The IBS-SSS evaluates the intensity of IBS symptoms during a ten-day period and includes assessments of abdominal pain, distension, stool frequency and consistency, and interference with patient quality of life, with each component graded via a visual analog scale. The IBS-SSS provides scores between 0 and 500 and categorizes patients as having mild (75-175), moderate (175-300), or severe (>300) IBS. [4]

Systematic Reviews

Ianiro et al (2019) performed a systematic review and meta-analysis to examine the efficacy of FMT as a treatment for IBS compared to either inactive placebo or autologous stool placebo.[51] Five RCTs enrolling 267 patients were included for analysis. Only 7.8% of the included patients had IBS-C. After study data were pooled, 79 (50%) of 158 patients assigned to donor FMT failed to respond, whereas 56 (51.4%) of 109 assigned to placebo failed to respond. Further characteristics and results are summarized in Tables 10 and 11. Study outcomes were mixed by

both routes of administration and assignment to treatment or placebo. When data from three RCTs utilizing autologous FMT as control groups were pooled, patients were more likely to experience an improvement in IBS symptoms with autologous FMT compared to donor FMT. While all studies utilized Rome III criteria for patient diagnosis and enrollment, not all studies utilized a validated IBS severity scoring system to quantify patient outcomes, limiting interpretation of results.

Elhusein et al (2022) conducted an updated systematic review and meta-analysis to assess the efficacy of FMT in treating patients with IBS.[52.] Nineteen studies (RCTs, single-arm trials, and observational studies) enrolling 928 patients were included in the systematic review; however, 12 studies (6 RCTs and 6 single-arm trials) were included in the analysis. Overall, FMT was significantly superior to placebo in IBS quality of life up to 24 weeks in the RCT analysis, with no difference between groups regarding IBS symptom improvement or improvement in the IBS Severity Scoring System. Analysis of single-arm trials revealed that the incidence of IBS symptom improvement with FMT was 57.8% (45.6% to 69.9%) with a reduction in the IBS Severity Scoring System and an improvement in quality of life through 24 weeks. Further study characteristics and RCT results are summarized in Tables 6 and 7. Larger RCTs with increased sample sizes and longer follow-up durations are necessary.

Wang et al (2023) performed a systematic review and meta-analysis of 9 RCTs (N=516) to investigate the efficacy and safety of FMT for IBS.[53.] The route of FMT administration included nasojejunal probe, gastroscope, colonoscopy, and oral capsules. Results demonstrated that when compared to placebo, a single FMT significantly decreased the IBS-SSS score (primary outcome) at months 1, 3, 6, 24, and 36. The clinical response rate was also significantly improved with FMT at months 3, 24, and 36 months, as was the IBS-QoL score at months 3, 24, and 36. Lastly, FMT did not increase the risk of adverse events. Further study characteristics and RCT results are summarized in Tables 10 and 11.

Table 10. Characteristics of Systematic Reviews

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Ianiro et al (2019)	To 2019	5	Patients with IBS, including IBS-D, IBS-C, and IBS-M, diagnosed with Rome III criteria	267 (17 to 86)	RCTs	12 weeks
Elhusein et al (2022)	To June 2021	19	Patients with IBS of any subtype	928 (10 to 165)	11 RCTs; 6 single-arm trials; 1 case series; 1 cohort study	Follow-up ranging from 1 to 12 months
Wang et al (2023)	To March 2023	9	Patients with moderate to severe IBS of any subtype diagnosed according to the Rome III or IV criteria	516 (8 to 165)	9 RCTs	Follow-up ranging from 1 to 12 months

IBS: irritable bowel syndrome; IBS-C: irritable bowel syndrome with constipation; IBS-D: irritable bowel syndrome with diarrhea; IBS-M: irritable bowel syndrome with mixed constipation and diarrhea; RCT: randomized controlled trial.

Table 11. SR & M-A Results

Study	IBS Symptoms Not Improving

Ianiro et al (2019)	
Overall	
Number of Patients, N (Trials)	267 (5)
Relative Risk (95% CI)	0.98 (0.58-1.66)
I^2 (p-Value)	NR
Route of Donor FMT Administration	
Oral Capsule: Number of Patients, N (Trials)	100 (2)
Relative Risk (95% CI)	1.96 (1.19 to 3.20)
I^2 (p-Value)	14% (.28)
Colonoscopy: Number of Patients, N (Trials)	103 (2)
Relative Risk (95% CI)	0.63 (0.43 to 0.93)
I^2 (p-Value)	0% (.71)
Nasojejunal Tube: Number of Patients, N (Trials)	64 (1)
Relative Risk (95% CI)	0.69 (0.46 to 1.02)
I^2 (p-Value)	NR
Placebo Type	
Inactive Placebo: Number of Patients, N (Trials)	100 (2)
Relative Risk (95% CI)	1.96 (1.19 to 3.20)
I^2 (p-Value)	14% (.28)
Autologous Stool: Number of Patients, N (Trials)	167 (3)
Relative Risk (95% CI)	0.66 (0.50 to 0.87)
I^2 (p-Value)	0% (.89)
Elhusein et al (2022)[41]	RCT analysis
After 4 weeks (FMT vs. placebo)	Improvement in IBS symptoms
Relative Risk (95% CI)	1.33 (0.22 to 7.89)
p-value	.75
After 12 weeks (FMT vs. placebo)	Improvement in IBS symptoms
Relative Risk (95% CI)	1.19 (0.67 to 2.13)
p-value	.55
After 4 weeks (FMT vs. placebo)	Change in IBS Severity Scoring System
Mean difference (95% CI)	-20 (-71.3 to 30.63)
p-value	.43
After 12 weeks (FMT vs. placebo)	Change in IBS Severity Scoring System
Mean difference (95% CI)	-30.79 (-99.45 to 37.96)
p-value	.38
After 24 weeks (FMT vs. placebo)	Change in IBS Severity Scoring System
Mean difference (95% CI)	6.49 (-74.81 to 87.79)

p-value	NR
After 4 weeks (FMT vs. placebo)	IBS-QOL
Mean difference (95% CI)	7.47 (2.05 to 12.89)
p-value	.04
After 12 weeks (FMT vs. placebo)	IBS-QOL
Mean difference (95% CI)	9.99 (5.78 to 14.19)
p-value	<.00001
After 24 weeks (FMT vs. placebo)	IBS-QOL
Mean difference (95% CI)	8049 (0.47 to 16.52)
p-value	.04
Wang et al (2023)	RCT analysis
After 4 weeks (FMT vs. placebo)	Change in IBS Severity Scoring System
Mean difference (95% CI)	-65.75 (-129.37 to -2.13)
p-value	.04
After 12 weeks (FMT vs. placebo)	Change in IBS Severity Scoring System
Mean difference (95% CI)	-102.11 (-141.98 to -62.24)
p-value	<.00001
After 24 weeks (FMT vs. placebo)	Change in IBS Severity Scoring System
Mean difference (95% CI)	-84.38 (-158.79 to -9.97)
p-value	.03
After 24 months (FMT vs. placebo)	Change in IBS Severity Scoring System
Mean difference (95% CI)	-110.41 (-145.37 to -75.46)
p-value	NR
After 36 months (FMT vs. placebo)	Change in IBS Severity Scoring System
Mean difference (95% CI)	-104.71 (-137.78 to -71.64)
p-value	NR

CI: confidence interval; NA: not applicable; NR: not reported.

Randomized Controlled Trials

Madsen et al (2021) reported the results of a double-blind RCT evaluating the efficacy of FMT capsules (n=26) versus placebo capsules (n=25) in patients with moderate-to-severe IBS (IBS-SSS score ≥175 points).[54] Both groups administered capsules for 12 days and patients were allowed to continue any concomitant IBS medications, including laxatives or agents for constipation. Patients tracked their symptoms in a diary and were followed for 6 months. The primary outcome was not specified, but investigators evaluated abdominal pain, stool frequency, and stool form. Subgroup analyses by IBS subtype were not performed.

Holvoet et al (2020) reported the results of a double-blind RCT evaluating the efficacy of FMT in patients with IBS-D or IBS-M and severe bloating (mean abdominal bloating sub-score of ≥3).[55] The intervention group (n=43) received donor FMT via the nasojejunal route and the control

group (n=19) received autologous FMT placebo via the same route. A daily symptom diary was used to assess IBS-related symptoms and improvement in IBS symptoms at 12 weeks was the primary outcome of the trial. After a single FMT, more patients in the treatment group versus placebo reported efficacy for more than 1 year (21% versus 5%). A second FMT reduced symptoms in 67% of patients with an initial response to donor stool, but not in patients with a prior non-response.

Lahtinen et al (2020) reported the results of a double-blind RCT evaluating the efficacy of FMT in patients with IBS.[56] The intervention group (n=23) received donor FMT via colonoscopy and the control group (n=26) received autologous FMT placebo via the same route. Approximately 35% of patients experienced adverse events with no significant difference between groups.

Characteristics and results of selected studies are summarized in Tables 12 and 13. Study relevance, design, and conduct limitations are summarized in Tables 14 and 15.

Table 12. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Madsen et al (2021)	Denmark	1	Oct to Dec 2016	Patients meeting Rome III criteria for IBS with moderate-to-severe disease activity (IBS-SSS ≥175 points)	n=25; 25 FMT capsules daily (containing a total of 12 g of fecal material) for 12 days	n=26; placebo capsules visually resembling fecal material for 12 days
Holvoet et al (2020)	Belgium	1	2015 to 2017	Patients meeting Rome III criteria for IBS; failed ≥3 conventional therapies for IBS; diarrhea-predominant or mixed-type IBS that had symptoms of severe bloating (mean abdominal bloating sub-score of ≥3)	n=43; donor FMT using fresh sample resuspended in 300 ml of sterile normal saline, filtered, and administered via nasojejunal route	n=19; autologous FMT placebo via nasojejunal route; 300 ml prepared fresh and stored frozen until treatment
Lahtinen et al (2020)	Finland	NR	NR	Patients meeting Rome III criteria for IBS	n=23; donor FMT; 30 g donor stool prepared fresh and stored frozen until treatment; delivered via colonoscopy	n=26; autologous FMT placebo prepared fresh; delivered via colonoscopy

IBS: irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Symptom Severity Scale; FMT: fecal microbiota transplantation; RCT: randomized controlled trial.

Table 13. Summary of Key RCT Results

Study	Participants	Change from Baseline

Madsen et al (2021)	Active (N)	Comparator (N)	Active	Comparator	p-Value
Decrease in abdominal pain at 6 months[1]	FMT capsule (25)	Placebo capsule (26)	-0.26	-0.53	0.27 (-1.17 to 1.72);
Decrease in stool frequency at 6 months[1]	FMT capsule (25)	Placebo capsule (26)	-0.34	-0.19	-0.14 (-0.76 to 0.47);
Decrease in weighted stool score at 6 months[1]	FMT capsule (25)	Placebo capsule (26)	-0.41	-0.04	-0.37 (-0.84 to 0.10);
Holvoet et al (2020)	**Active (N)**	**Comparator (N)**	**Active**	**Comparator**	**p-Value**
Improvement of IBS symptoms and bloating at 12 weeks	Donor FMT (43)	Autologous FMT placebo (19)	24/43 (56)	5/19 (26)	p=0.03
Lahtinen et al (2020)	**Active (N)**	**Comparator (N)**	**Active**	**Comparator**	**p-Value**
Decrease in IBS-SSS score ≥50 points at 12 weeks	Donor FMT (23)	Autologous FMT placebo (26)	11/23 (48)	11/26 (42)	NS
Decrease in IBS-SSS score ≥50 points at 52 weeks	Donor FMT (23)	Autologous FMT placebo (26)	NR	NR	NS

GSRS-IBS: Gastrointestinal Symptom Rating Scale for IBS; IBS: irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Symptom Severity Scale; FMT: fecal microbiota transplantation; IQR: interquartile range; NR: not reported; NS: not significant; RCT: randomized controlled trial.
[1] Response was defined as decrease in IBS-SSS score of 75 points or more.

Table 14. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Madsen et al (2021)				1, 5. A clinically significant difference was not prespecified for the primary outcome; safety outcomes were not reported	
Holvoet et al (2020)	4. Rationale for excluding individuals with IBS with constipation was not provided	1. FMT products were not prepared with a standard amount of autologous stool	1. placebo FMT products were not prepared with a standard amount of autologous stool	4. Primary outcome measure was not established and validated measurements; 5. A clinically significant difference was not prespecified for the primary outcome	
Lahtinen et al (2020)			1. placebo FMT products were not prepared with a standard amount of autologous stool		

FMT: fecal microbiota transplantation; IBS: irritable bowel syndrome; SSRI: selective serotonin reuptake inhibitors.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 15. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Madsen et al (2021)						
Holvoet et al (2020)	3. Allocation concealment unclear				1. Power calculations not reported	
Lahtinen et al (2020)						3. The number of patients achieving the primary outcome was not reported; confidence intervals and p-values not reported for all outcomes

FMT: fecal microbiota transplantation; IBS-SSS: Irritable Bowel Syndrome Symptom Severity Scale.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. No intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Irritable Bowel Syndrome

For individuals who have IBS who receive FMT, the evidence includes a systematic review and RCTs. One systematic review with meta-analysis involving 19 studies reported that FMT was superior to placebo in improving quality of life through 24 weeks. Conversely, a systematic review with meta-analysis of 9 RCTs found that a single FMT significantly decreased the IBS-SSS score at 1, 3, 6, 24, and 36 months compared to placebo. Another systematic review with meta-analysis reviewed 5 RCTs and reported mixed outcomes for FMT in patients with IBS. When all studies were pooled, no net benefit was found for active FMT. In a pooled analysis of 3 RCTs utilizing autologous FMT as a placebo, patients were less likely to experience an improvement in IBS symptoms with donor FMT (i.e., active treatment). Two additional RCTs also utilized autologous FMT as a placebo, and did not find a significant reduction in symptoms of IBS using donor FMT; both trials also found reduced durability of response 1 year following donor FMT. An additional placebo-controlled RCT used FMT delivered via oral capsules and found no improvement in

abdominal pain scores, stool frequency, or stool form in a mixed population of patients with IBS. Few treatment-related adverse events have been reported. Data are limited by small study sizes and heterogeneity in utilized outcome measurement scales and definitions of treatment response.

Pouchitis, Constipation, Multi-Drug Resistant Organism Infection, or Metabolic Syndrome

Clinical Context and Therapy Purpose
The purpose of FMT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with pouchitis, constipation, MDRO infection, or metabolic syndrome.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant populations of interest are individuals with pouchitis, constipation, MDRO infection, or metabolic syndrome.

Interventions
The therapy being considered is FMT. Patients with pouchitis, constipation, MDRO infection, or metabolic syndrome are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Comparators
The following therapy is currently being used to treat pouchitis, constipation, MDRO infection, and metabolic syndrome: standard of care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Though not completely standardized, follow-up for pouchitis, constipation, MDRO infection, or metabolic syndrome symptoms would typically occur in the months to years after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the same principles as outlined for indication 1.

Systematic Reviews
A systematic review by Rossen et al (2015) of studies on FMT identified a case series on constipation (n=3 patients) and another on pouchitis (n=8 patients).[57] Additional systematic reviews by Cold et al (2020) (N=69) and Zaman et al (2023) (N=103) evaluating FMT treatment in patients with chronic pouchitis both concluded that the use of FMT in this population requires further study before incorporation into clinical practice.[58,59]

A systematic review by Saha et al (2019) identified 21 studies (N=192) on FMT in preventing multidrug-resistant infections and/or its effect on MDRO colonization.[60] Only 1 of the studies was an RCT (see Huttner et al summary under Randomized Controlled Trials), 7 were uncontrolled clinical trials, 2 were retrospective cohort studies, and 11 were case series or case reports. The MDRO eradication rate ranged from 0 to 100% using all included data; when excluding data from

case series and case reports, the eradication rate ranged from 37.5% to 87.5%. No serious adverse events from FMT were reported. The authors concluded that more data are needed before FMT can be applied in clinical practice as a treatment for eradicating MDR colonization and preventing recurrent MDR infections.

A systematic review and meta-analysis by Proenca et al (2020) searched for RCTs assessing the use of FMT in obese and metabolic syndrome patients.[61] Six RCTs (N=154) were included in the meta-analysis, of which 5 studies assessed the role of FMT for metabolic syndrome in obesity and 1 assessed the role of FMT in obese patients without metabolic syndrome. Two to 6 weeks after intervention, patients in the FMT group had a lower mean concentration of glycated hemoglobin than the placebo group (mean difference [MD], -1.69 mmol/L; 95% CI, -2.81 to -0.56; p=0.003) and higher mean high-density lipoprotein (HDL) cholesterol than the placebo group (MD, 0.09 mmol/L; 95% CI, 0.02 to 0.15; p=0.008); the placebo group had lower mean low-density lipoprotein (LDL) cholesterol than the FMT group (MD, 0.19 mmol/L; 95% CI, 0.05 to 0.34; p=0.008). Fasting glucose, triglycerides, and total cholesterol did not differ between groups after 2 to 6 weeks. At 12 weeks after treatment, there was no statistically significant difference between FMT and placebo for the following outcomes: concentration of glycated hemoglobin, fasting glucose, LDL cholesterol, HDL cholesterol, and triglycerides. The authors concluded that more data are needed before FMT can be applied in clinical practice as a treatment for metabolic syndrome. Similar findings were seen in a more recent systematic review and meta-analysis by Qui et al (2023), which included 9 RCTs (N=303) investigating the role of FMT in the treatment of obesity and/or metabolic syndrome.[62.] In the short-term (<6 weeks after FMT), patients in the FMT group exhibited lower fasting glucose (MD, -0.12 mmol/L; 95% CI, -0.23 to -0.01), HbA1c (MD, -0.37 mmol/mol; 95% CI, -0.73 to -0.01), and insulin levels (MD, -24.77 mmol/L; 95% CI, -37.60 to -11.94), as well as higher HDL cholesterol levels (MD, 0.07 mmol/L; 95% CI, 0.02 to 0.11). Longer-term outcomes (≥12 weeks) did not differ between FMT and placebo groups, nor did FMT-related adverse events.

Randomized Controlled Trials

Karjalainen et al (2021) assessed the efficacy and safety of FMT in the treatment of chronic pouchitis via a single-center, double-blind, parallel-group trial with a 52-week follow-up.[63] Twenty-six patients were randomly allocated to FMT from a healthy donor (n=13) or autologous FMT as the placebo (n=13). The study protocol included 2 FMTs into the pouch on weeks 0 and 4. Results revealed that relapse occurred in 9 patients in the intervention group versus 8 in the placebo group during the 52-week follow-up (hazard ratio [HR], 1.90; 95% CI, 0.75 to 4.98; p=.190). However, 5 patients in the FMT group relapsed even before the second transplant, whereas no patient relapsed in the placebo group during the initial 4 weeks. No major adverse effects were reported. The FMT regimen evaluated in this study was not effective for the treatment of chronic pouchitis.

An RCT by Huttner et al (2019) evaluated the superiority of a 5-day course of antibiotic therapy followed by FMT (n=22) for the treatment of MDROs compared to no intervention (n=17).[64] Patients with either extended-spectrum beta-lactamase-producing Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae were enrolled. In the intention-to-treat analysis, 9/22 (41%) of patients assigned to the intervention group were negative for both extended-spectrum beta-lactamase-Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae compared to 5/17 (29%) of patients in the no-intervention control arm at follow-up days 35-48. No superior benefit was observed with an odds ratio for decolonization success of 1.7 (95% CI: 0.4 to 6.4).

Cohort Studies
Bar-Yoseph et al (2021) evaluated FMT for carbapenemase-producing *Enterobacteriaceae* (CPE) eradication.[65] A total of 15 patients who were CPE carriers were prospectively enrolled and received encapsulated FMT (15 capsules daily) for 2 days, of which 13 patients completed treatment. Eradication of CPE at 1 month (defined as 3 negative swab cultures plus negative polymerase chain reaction for carbapenemase gene) occurred in 9/13 patients (69.2%). The authors noted that the quantity of *Enterobacteriaceae* decreased in post-FMT samples of the responders but increased among failures.

Seong et al (2020) evaluated FMT for patients colonized with CPE and/or vancomycin-resistant enterococci (VRE).[66] A total of 35 patients were prospectively enrolled and underwent donor FMT via colonoscopy: 4 for CPE, 19 for VRE, and 12 for combined CPE and VRE. Within 1 year of receiving FMT, 24 (68.6%) patients were decolonized. Recolonization occurred in 9 patients at a median time of 55 days following FMT.

Section Summary: Pouchitis, Constipation, MDRO Infection, or Metabolic Syndrome
For individuals who have pouchitis, constipation, MDRO infection, or metabolic syndrome who receive FMT, the evidence includes systematic reviews and an RCT. Systematic reviews of data from patients who received FMT for constipation, pouchitis, MDROs, and metabolic syndrome have all concluded that more data are needed before FMT can be applied in clinical practice for these populations. In a meta-analysis assessing the use of FMT in obese and metabolic syndrome patients, the initial improvements of several metabolic parameters failed to demonstrate sustained durability at 12 weeks after treatment. While cohort studies have demonstrated FMT to be fairly effective in eradicating MDRO colonization, a RCT comparing FMT to no intervention in patients with MDROs failed to demonstrated improved rates of decolonization with treatment. An additional RCT in patients with chronic pouchitis concluded that the FMT regimen evaluated was not effective.

ADVERSE EVENTS
In 2016, Wang et al published a systematic review of adverse effects associated with fecal microbiota transplantation.[67] The authors identified 50 publications with a total of 1089 FMT-treated patients. Of these, 831 patients were affected by CDI, 235 had IBD, and the remainder had various miscellaneous indications. The overall incidence of adverse events in the studies was 28.5% (310/1089). Most reported adverse events were of mild to moderate severity and included abdominal cramping, flatulence, fever and belching. A total of 9.2% (100/1089) patients developed serious adverse events. Thirty-eight patients died. One death was deemed by Wang et al to be definitely related to FMT, 2 were possibly related and 35 were unrelated. The death that was definitely related was due to aspiration during colonoscopy sedation and the 2 possibly related deaths were associated with infections due either to FMT or the patients' immunocompromised state. The incidence of severe infection was 2.5% (27/1089). The authors categorized 8 cases of severe infection was probably or possibly related to FMT and the other 19 cases as unrelated.

SUMMARY OF EVIDENCE
For individuals who have recurrent *Clostridioides difficile* infection (CDI) refractory to antibiotic therapy who receive fecal microbiota transplantation (FMT) with a product that is not commercially available, the evidence includes systematic reviews with meta-analyses and observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Meta-analyses have found that FMT is more effective than standard treatment or placebo for patients with recurrent CDI. A long-term prospective study found that FMT for

recurrent or refractory CDI appears to be durable at 4 to 8 years following treatment, even for patients who had subsequently received non-CDI antibiotic therapy. A meta-analysis comparing several routes of FMT delivery for the treatment of recurrent CDI found that cure rates were significantly higher with colonoscopy or oral capsules versus nasogastric tube or enema, while colonoscopy and capsules were equally effective. Similar success rates have been demonstrated with FMT using fresh versus frozen feces. Conversely, data regarding the superiority of FMT using donor versus autologous feces are conflicting. Few treatment-related adverse events have been reported. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have recurrent *Clostridioides difficile* infection (CDI) refractory to antibiotic therapy who receive fecal microbiota transplantation (FMT) with a commercially available Food and Drug Administration (FDA)-approved product, the evidence includes RCTs and an observational study. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The efficacy of a commercially available rectally administered suspension containing live fecal microbiota spores was evaluated in a phase 3 double-blind, placebo-controlled RCT (PUNCH CD3; N=289), with analysis conducted using a Bayesian hierarchical model that borrowed data from a preceding phase 2b trial (PUNCH CD2; N=134). Both trials included adults with recurrent CDI (1 or more recurrences in PUNCH CD3, and 2 or more recurrences in PUNCH CD2) or a minimum of 2 CDI episodes within the preceding year that led to hospitalization, who received at least 10 consecutive days of standard antibiotic therapy and displayed improvement in CDI symptoms. The rate of treatment success, defined as the absence of CDI within 8 weeks of study treatment, was significantly higher in the group of patients who received rectally administered live fecal microbiota spores as compared to placebo (70.6% vs 57.5%). Additionally, among those patients who achieved treatment success at 8 weeks, more than 90% remained free of CDI recurrence through 6 months. A phase 3, double-blind, placebo-controlled RCT (N=182) evaluated the efficacy of commercially available oral capsules containing live fecal microbiota spores in patients who had at least 2 recurrences within 12 months and who received 10 to 21 consecutive days of standard antibiotic therapy and displayed improvement in CDI symptoms. Results demonstrated that a 3-day course of oral live fecal microbiota spores was more effective than placebo at preventing CDI recurrence within 8 weeks of treatment (12% vs 40%, respectively). In a single-arm, open-label trial evaluating commercially available oral capsules containing live fecal microbiota spores, the CDI recurrence rate at 24 weeks follow-up was 13.7%. Both commercially available therapies were well-tolerated, with the majority of adverse events being mild-to-moderate in severity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have inflammatory bowel disease (IBD) who receive FMT, the evidence includes systematic reviews and randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Systematic reviews have generally shown favorable clinical remission and response with FMT in patients with IBD while acknowledging that further RCTs and long-term follow-ups are needed to assess long-term effectiveness and safety. Additionally, a Cochrane review found that FMT did not significantly improve the maintenance of clinical or endoscopic remission of ulcerative colitis (UC). A 48-week RCT in patients with UC in clinical remission after prior FMTs found conflicting results for remission outcomes with additional courses of FMT. Another RCT in patients with recurrent active UC found a median remission time of 24 months in both FMT and standard of care treatment groups. A 12-month RCT evaluating FMT for the maintenance of remission in patients with UC did not find a statistically significant difference between single-dose FMT and control groups. This

current evidence is not sufficient to permit conclusions on the efficacy of FMT for UC. Additionally, questions remain about the optimal route of administration, donor characteristics, and the number of transplants. A small RCT in patients with Crohn disease (CD) failed to find a difference in the achievement of remission with FMT versus placebo. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have irritable bowel syndrome (IBS) who receive FMT, the evidence includes systematic reviews and RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. For individuals who have IBS who receive FMT, the evidence includes systematic reviews and RCTs. One systematic review with meta-analysis involving 19 studies reported that FMT was superior to placebo in improving quality of life through 24 weeks; however, there was no difference in the IBS Severity Scoring System (IBS-SSS) or symptom improvement between FMT and placebo. Conversely, a systematic review with meta-analysis of 9 RCTs found that a single FMT significantly decreased the IBS-SSS score at 1, 3, 6, 24, and 36 months compared to placebo. Another systematic review with meta-analysis reviewed 5 RCTs and reported mixed outcomes for FMT in patients with IBS. When all studies were pooled, no net benefit was found for active FMT. In a pooled analysis of 3 RCTs utilizing autologous FMT as a placebo, patients were less likely to experience an improvement in IBS symptoms with donor FMT (i.e., active treatment). Two additional RCTs also utilized autologous FMT as a placebo, and did not find a significant reduction in symptoms of IBS using donor FMT; both trials also found reduced durability of response 1 year following donor FMT. An additional placebo-controlled RCT used FMT delivered via oral capsules and found no improvement in abdominal pain scores, stool frequency, or stool form in a mixed population of patients with IBS. Few treatment-related adverse events have been reported. Data are limited by small study sizes and heterogeneity in utilized outcome measurement scales and definitions of treatment response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pouchitis, constipation, multi-drug resistant organism (MDRO) infection, or metabolic syndrome who receive FMT, the evidence includes systematic reviews, RCTs, and prospective cohort studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Systematic reviews of data from patients who received FMT for constipation, pouchitis, MDRO infections, and metabolic syndrome have all concluded that more data are needed before FMT can be applied in clinical practice for these populations. In a meta-analysis assessing the use of FMT in obese and metabolic syndrome patients, the initial improvements of several metabolic parameters failed to demonstrate sustained durability at 12 weeks after treatment. While cohort studies have demonstrated FMT to be fairly effective in eradicating MDRO colonization, a RCT comparing FMT to no intervention in patients with MDROs failed to demonstrate improved rates of decolonization with treatment. An additional RCT in patients with chronic pouchitis concluded that the FMT regimen evaluated was not effective. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12.

Table 16. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT03931941	Microbiota Restoration Therapy for Recurrent Clostridium Difficile Infection (PUNCH CD3-OLS) (CD3-OLS)	550	Sept 2023 (active, not recruiting)
NCT05831189	A Multi-center, Single-arm Trial Exploring the Safety and Clinical Effectiveness of RBX2660 Administered by Colonoscopy to Adults With Recurrent Clostridioides Difficile Infection (CDI-SCOPE)	40	July 2023 (recruiting)
NCT04997733	Fecal Microbiota Transplantation in Crohn's Disease as Relay After Anti-TNF Withdrawal (MIRACLE)	150	Jan 2026
NCT04691544	Donor Versus Autologous Fecal Microbiota Transplantation for Irritable Bowel Syndrome: a Double Blind, Placebo-Controlled, Randomized Trial	450	Dec 2027 (recruiting)
NCT05035342	Fecal Transplantation to Eradicate Colonizing Emergent Superbugs (FECES)	214	Jan 2026 (Not yet recruiting)
NCT04970446	The MIRO II Study: Microbial Restoration in Inflammatory Bowel Diseases	120	Dec 2025
NCT02269150	A Randomized Controlled Trial of Autologous Fecal Microbiota Transplantation (Auto-FMT) for Prophylaxis of Clostridium Difficile Infection in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation	59	Oct 2025
NCT03562741	Outcomes and Data Collection for Fecal Microbiota Transplantation for the Treatment of Recurrent Clostridium Difficile	500	Jan 2025
NCT03804931	Efficacy and Safety of Fecal Microbiota Transplantation for Ulcerative Colitis	120	Dec 2030
NCT03613545	Efficacy and Safety of Fecal Microbiota Transplantation for Irritable Bowel Syndrome	120	Dec 2030
NCT04521205	A Multicenter Clinical Trial: Efficacy, Safety of Fecal Microbiota Transplantation for Inflammatory Bowel Disease	200	Apr 2024
Unpublished			
NCT02255305	Fecal Microbiota Transplantation Versus Standard Medical Therapy for Initial Treatment of Recurrent Clostridium Difficile Infection	60	Dec 2019
NCT02592343	Prospective, Open-label Trial to Evaluate Efficacy of Lyophilized Fecal Microbiota Transplantation for Treatment of Recurrent C. Difficile Infection	100	Mar 2020
NCT04100291	The Effect of Faecal Microbiota Transplantation in the Treatment of Chronic Pouchitis: A Multicentre, Placebo-controlled, Randomized, Double Blinded Trial	50	Dec 2021 (terminated)
NCT04746222	Oral Capsule-administered Faecal Microbiota Transplantation for Intestinal Carbapenemase-producing Enterobacteriaceae Decolonization	108	Jul 2023 (Not yet recruiting)

NCT: national clinical trial

SUPPLEMENTAL INFORMATION

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, BCBSA received input from 5 clinicians at 2 academic medical centers and 5 clinicians associated with 3 physician specialty societies when this policy was under review in 2014. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was

near-consensus agreement that fecal transplantation may be considered medically necessary for treating at least some patients with CDI. In addition, there was near-consensus that FMT is considered investigational for inflammatory bowel diseases and consensus that it is considered investigational for conditions other than those previously mentioned. Input was mixed on criteria to use for selecting patients with CDI for fecal transplantation; in general, number of recurrences was considered an important criterion. There was near-consensus among reviewers that there are potential safety concerns associated with FMT and that these should be studied further before the procedure is offered routinely in clinical practice.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Gastroenterology (ACG)

In 2019, the American College of Gastroenterology published guidelines on the management of adults with ulcerative colitis.[35] The guidelines addressed FMT as therapy for induction of remission, as follows: “Fecal microbiota transplantation (FMT) requires more study and clarification of treatment before use as therapy for UC.”

In 2021, the ACG published guidelines on the prevention, diagnosis, and treatment of *Clostridioides difficile* infection (CDI).[13] This guideline makes the following recommendations:

- “We suggest fecal microbiota transplantation (FMT) be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, particularly, when patients are deemed poor surgical candidates (strong recommendation, low quality of evidence).”
- “We recommend patients experiencing their second or further recurrence of CDI be treated with FMT to prevent further recurrences (strong recommendation, moderate quality of evidence).”
- “We recommend FMT be delivered through colonoscopy (strong recommendation, moderate quality of evidence) or capsules (strong recommendation, moderate quality of evidence) for treatment of CDI; we suggest delivery by enema if other methods are unavailable (conditional recommendation, low quality of evidence).”
- “We suggest repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT (conditional recommendation, very low quality of evidence).”
- “FMT should be considered for recurrent CDI in patients with IBD (strong recommendation, very low quality of evidence).”

The guidelines define a recurrent CDI as the recurrence of diarrhea and a confirmatory positive test (NAAT or EIA) within 8 weeks after treatment of an initial episode of CDI.

In 2021, the ACG also published a guideline on the management of irritable bowel syndrome (IBS).[49] This guideline recommended against the use of fecal transplant for the treatment of global IBS symptoms (strong recommendation; very low quality of evidence).

American Society of Colon and Rectal Surgeons (ASCRS)

In 2021, the American Society of Colon and Rectal Surgeons (ASCRS) clinical practice guidelines for the management of *Clostridiodes difficile* infection recommends[12]:

- "Patients with recurrent or refractory CDI should typically be considered for fecal bacteriotherapy (e.g., intestinal microbiota transplantation) if conventional measures, including appropriate antibiotic treatment, have failed (Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B)."

- "Patients with 3 or more CDI episodes can be managed with a vancomycin tapered and pulsed course or fidaxomicin followed by a microbiome-based therapy such as fecal microbiota transplantation."
- "In general, conventional antibiotic treatment should be used for at least 2 recurrences (i.e., 3 CDI episodes) before offering fecal microbiota transplantation."

Per Table 3 in this guideline: for "Third or Subsequent" CDI episode: "If FMT is available, then 10-day course of vancomycin followed by FMT."

Infection Diseases Society of America
The Infectious Diseases Society of America and Society for Healthcare Epidemiology of America updated clinical practice guidelines (2019) for the diagnosis and treatment of CDI in children and adults.[10] Recommendations were summarized as follows:

"Consider fecal microbiota transplantation for pediatric patients with multiple recurrences of CDI following standard antibiotic treatments. (Weak recommendation, very low quality of evidence)"

"Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments. (Strong recommendation, moderate quality of evidence)"

"Potential candidates for FMT include patients with multiple recurrences of CDI who have failed to resolve their infection despite treatment attempts with antibiotic agents targeting CDI. Although there are no data to indicate how many antibiotic treatments should be attempted before referral for FMT, the opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried."

A 2021 focused update of this guideline echoes the previous recommendations for FMT by stating: "FMT is recommended only for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments and where appropriate screening of donor and donor fecal specimens have been performed, in accordance with these newer FDA recommendations."[11]

The FDA safety alerts regarding the use of FMT are summarized in the Policy Guidelines and Background sections of this document.

Government Regulations
National and local:

There is no national or local coverage determination on this topic. Medicare has a national fee for G0455 listed when done in the facility, and a fee when done in a non-facility setting. 44705 is listed with a PFS procedure status of "I" indicating the code is not valid for Medicare purposes.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/13	4/16/13	4/22/13	Joint policy established
7/1/14	4/8/14	4/15/14	Routine update. Policy reformatted to match BCBSA policy. Added NOC code to policy.
9/1/15	6/16/15	7/16/15	Routine maintenance.
9/1/16	6/21/16	7/25/16	Routine maintenance, updated references and rationale sections. Added to policy statement.
9/1/17	6/20/17	6/20/17	Routine maintenance. Added references 9, 13 and 20.
9/1/18	6/19/18	6/19/18	Routine policy maintenance, added reference # 7. No change in policy statement.
9/1/19	6/18/19		Routine policy maintenance. Added references 6, and 14-16.
9/1/20	6/16/20		Routine policy maintenance. Updated rationale section, added study charts, added references 7, 23, 25-27 and 32. No change in policy status.
9/1/21	6/15/21		MPS updated with information from 2017 IDSA guidelines for C.diff regarding the number of prior CDIs before FMT is considered, and FDA warning regarding donor screening and testing of donor stool. Added references #9, 22, 27, 30, 31, 33, 34, 36 and 38.
9/1/22	6/21/22		Updated rationale section, added references 1-3, 22, 33-34 and 41. Inclusion section re-structured.
9/1/23	6/13/23		Added code 0780T as E/I. Updated rationale section, added references 29,30,41 and 49. No change in policy status. Vendor managed: N/A. (ds)
9/1/24	6/14/24		Inclusion/Exclusion section revised to include compounded and FDA

			approved product. Rationale updated, references added supporting FDA approved products for FMT. Code 0780T now established. Vendor managed: N/A (ds)

Next Review Date: 2nd Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: FECAL MICROBIOTA TRANSPLANTATION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply,
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service. *Medicare covers this procedure under G0455*

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.