Fecal Microbiota Transplantation

Policy Number: CS368.B
Effective Date: April 1, 2024

Instructions for Use

Table of Contents **Page**

Related Community Plan Policies

- Fecal Calprotectin Testing
- Outpatient Surgical Procedures – Site of Service
- Rebyota™ (Fecal Microbiota, Live-Jslm)

Commercial Policy

- Fecal Microbiota Transplantation

Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	None
Kentucky	Fecal Microbiota Transplantation(for Kentucky Only)
Louisiana	Fecal Microbiota Transplantation (for Louisiana Only)
New Jersey	Fecal Microbiota Transplantation (for New Jersey Only)
North Carolina	Fecal Microbiota Transplantation (for North Carolina Only)
Ohio	Fecal Microbiota Transplantation (for Ohio Only)
Pennsylvania	Fecal Microbiota Transplantation (for Pennsylvania Only)
Tennessee	Fecal Microbiota Transplantation (for Tennessee Only)

Coverage Rationale

Note: This policy does not apply to members ages < 18 years or to routes of administration other than enema for Fecal Microbiota Transplantation.

Fecal Microbiota Transplantation (FMT) via enema is proven and medically necessary for prevention of the recurrence of Clostridioides Difficile Infection (CDI) when all the following criteria are met:

- The individual has had two or more recurrences of CDI following the initial Episode; and
- The infection has been confirmed by the recurrence of diarrhea and a positive stool test for Clostridioides difficile toxin; and
- The individual has had antibiotic therapy for at least two Episodes of recurrence after the initial Episode

FMT is unproven and not medically necessary for prevention and/or treatment for all other indications, including but not limited to, ulcerative colitis (UC), Crohn's disease (CD), and irritable bowel syndrome (IBS) due to insufficient evidence of efficacy.

Definitions

Clostridium Difficile Infection (CDI): Clostridioides difficile, formerly known as Clostridium difficile, is an anaerobic, gram-positive, bacillus bacterium that can be a normal inhabitant of the human colon and is most commonly transmitted via a fecal-oral route (Poylin et al., 2021).

Episode of CDI: An Episode of CDI is considered clinical findings compatible with CDI and microbiological evidence of Clostridioides difficile-free toxins by enzyme immunoassay without reasonable evidence of another cause of diarrhea or a clinical picture compatible with CDI and a positive nucleic acid amplification test (NAAT), preferably with a low cycle threshold (Ct) value or positive toxigenic Clostridioides difficile culture or pseudomembranous colitis as diagnosed during endoscopy, after colectomy or on autopsy, in combination with a positive test for the presence of toxigenic Clostridioides difficile (van Prehn et al., 2021).

Fecal Microbiota Transplantation (FMT): FMT is a microbial-based therapy in which prepared stool from a healthy donor is transferred to an individual with a disease. It has become part of the clinical algorithm to treat Recurrent CDIs (Brook et al., 2022).

Recurrent CDI (rCDI): rCDI is the recurrence of diarrhea and a positive stool test for Clostridioides difficile toxin either occurring within 8 weeks following treatment or as diagnosed by a GI or ID specialist (Kelly et al., 2021). Although most recurrences occur within two to eight weeks after treatment, recurrences are known to occur later than that time frame.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0780T	Instillation of fecal microbiota suspension via rectal enema into lower gastrointestinal tract
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen

HCPCS Code	Description
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen

Description of Services

Fecal Microbiota Transplantation (FMT) involves introducing saline-diluted fecal matter (i.e., fecal suspension) from a donor into the gastrointestinal tract of an individual with Recurrent Clostridium Difficile Infection (rCDI) with the intent of reestablishing a more normal fecal composition and increased microbial diversity.

The treatment has been used extensively for treating rCDI with success, likely because the donated gut microbial ecosystem can substitute the microbiota lost through antibiotic use and consequently suppress Clostridioides difficile overgrowth, promoting recovery. Donor strains introduced into the gastrointestinal tract via FMT robustly colonize and create themselves in conjunction with, or in place of, the pre-existing microbiota (Carlucci et al., 2016).

Fecal Microbiota Transplantation (FMT) for Treating Recurrent Clostridium Difficile Infection (rCDI)

In 2023, ECRI created a clinical evidence assessment on Rebyota (Ferring Pharmaceuticals, Inc.) for preventing rCDI. The assessment uncovered one randomized controlled trial (RCT), two case series, and two cost studies. There was no evidence bar associated with the assessment, however, the studies uncovered showed support for FMT for preventing rCDI.

Garey et al. (2023) evaluated disease-specific health-related quality of life (HRQL) for individuals with rCDI treated with fecal microbiota, live-jslm [REBYOTA (RBL); Rebiotix] versus placebo through a secondary analysis of a randomized, double-blind, placebo-controlled phase 3 study (PUNCH CD3). Changes in a disease specific Clostridioides difficile Quality of Life Survey (Cdiff32) total and domain scores from baseline to week eight were collected and compared between RBL and placebo for responders and nonresponders. The results of the study demonstrated findings analyzed for a total of 185 participants [RBL, n = 128 (69.2%); placebo, n = 57 (30.8%)] with available Cdiff32 data. Individuals from both arms showed significant improvements in Cdiff32 scores relative to baseline across all outcomes and at all time points (all $p < .001$); RBL-treated showed significantly more improvements in the mental domain than those receiving placebo. In an adjusted analysis, RBL-treated people showed more significant improvements than placebo in total score and physical and mental domains (all $p < .05$). Similar improvement in the mental domain was observed among responders. In contrast, nonresponders showed numerical improvements with RBL but not placebo. Limitations include the loss of considerable sample size owing to the open-label treatment choice for nonresponders, and because those enrolled in clinical trials may differ from those in practice, the generalizability of the study results may be limited. The authors concluded that the RBL-treated individuals reported more substantial and sustained disease-specific HRQL improvements than placebo-treated individuals (Included in ECRI, 2023).

ECRI developed a clinical evidence assessment on FMT for treating rCDI in 2018; updated 2023. The evaluation uncovered a large body of favorable evidence from numerous clinical studies synthesized in meta-analyses strongly supporting FMT's safety and effectiveness as a first-line treatment for rCDI. Eight evidence-based clinical guidance documents and four other documents from medical societies, public health agencies, and healthcare systems endorse FMT for treating rCDI and primary or rCDI resistant to antibiotic therapies. There was no change in the evidence bar from the update in 2023.

Through a randomized, double-blind, placebo-controlled trial (EarlyFMT), Baunwall and associates (2022) compared the efficacy and safety of FMT with a placebo after vancomycin for first or second clostridium difficile infection (CDI). Individuals aged 18 and over who had first or second CDI (defined as more than three watery stools) per day and a positive c difficile PCR test were randomized 1:1 to either FMT or placebo administered on day one and between day three and seven after they had received 125 mg oral vancomycin four times daily for ten days. The primary outcome measured was the resolution of CDI associated diarrhea eight weeks following treatment, as participants were followed up for eight weeks or until recurrence. The primary outcome and safety outcomes were analyzed in the intention-to-treat group, which included all randomly assigned individuals. The trial resulted in the consecutive screening of 86 individuals, of whom 42 were randomly assigned to FMT (n = 21) or placebo (n = 21). The trial was stopped after the interim analysis on April 7, 2022, for ethical reasons because a significantly lower resolution rate was identified in the placebo group compared with the FMT group (Haybittle-Peto boundary limit $p < 0{\cdot}001$). 19 (90%; 95% CI 70-99) of 21 participants in the FMT group and seven (33%, 95% CI 15-57) of 21 people in the placebo group had a resolution of C difficile-associated diarrhea (CDAD) at week 8 ($p = 0{\cdot}0003$). The absolute risk reduction was 57% (95% CI 33-81). Overall, 204 adverse events occurred, with one or more reported in 20 of 21 people in the FMT group and all 21 in the placebo group. Diarrhea (n = 23 in the FMT group; n = 14 in the placebo group) and abdominal pain (n = 14 in the FMT group; n = 11 in the placebo group) were the most common adverse events. Three serious adverse events possibly related to study treatment occurred (n = 1 in the FMT group; n = 2 in the placebo group), but no deaths or colectomies during the 8-week follow-up. The authors concluded that for individuals with first or second CDI, first-line FMT is highly effective and superior to the standard of care vancomycin alone in achieving sustained resolution from CDI. The trial is registered with ClinicalTrials.gov, NCT04885946.

In 2022, Khanna et al. steered a phase III, randomized, double-blind, placebo-controlled trial (PUNCH CD3) with a Bayesian Primary Analysis on the efficacy and safety of RBX2660 for the prevention of rCDI. Included in the trial were individuals 18 years or older with one or more CDI recurrences, a positive stool assay for CDI and previous treatment with standard-of-care antibiotics. Randomly assigned were 267 individuals 2:1 to receive a placebo or RBX2660 single dose enema (n = 180, RBX2660; n = 87, placebo) after blinding. The outcome measured was treatment success, defined as the absence of CDI after eight weeks. The number of participants with treatment success at eight weeks, remaining CDI recurrence free, was about 90%

for both treatment groups. Overall, 65 participants received a second treatment course (open-label RBX2660) after confirmed treatment failure. Of the 24 participants treated with a blinded placebo who were subsequently treated with open-label RBX2660, 15 (62.5%) attained treatment success within eight weeks. All 15 of these participants had sustained responses through 6 months. Of the 41 participants treated with blinded RBX2660 with open-label RBX2660, 22 (53.7%) attained treatment success within eight weeks. Of these 22 participants, 19 (86%) had a sustained response through 6 months. In total, 68 of 85 (80%) participants who received a blinded placebo and 148 of 177 (83.6%) participants who received blinded RBX2660 achieved treatment success by their second course (i.e., open-label RBX2660). Limitations included the inability to generalize the data broadly; the study population was limited to those with rCDI. The authors concluded RBX2660 demonstrated superiority as a treatment to decrease rCDI proceeding standard of care antibiotic treatment. There were no treatment-related severe adverse reactions, showing RBX2660 was well tolerated. The results confirm earlier evidence of the positive benefits of RBX2660 on the reduction of CDI recurrence in adults after antibiotic treatment for rCDI.

In 2022, Orenstein reported on the results from a prospective, multicenter open-label phase two clinical trial on the durable reduction of CDI recurrence and microbiome restoration after treatment with RBX2660. The trial enrolled individuals with two or more recurrences of CDI and treated with standard-of-care antibiotic therapy after a CDI episode or greater than two episodes of severe CDI requiring hospitalization. Administration of RBX2660 was given with doses seven days apart, and treatment success was defined as the absence of CDI diarrhea or the need for retreatment for eight weeks after completing treatment. A historical control group was identified from a retrospective chart review of participants treated with standard-of-care antibiotics for rCDI, and the primary objective was comparing the treatment success of RBX2660 to the control group. In this phase two open-label clinical trial, RBX2660 demonstrated a 78.9% (112/142) treatment success rate compared to a 30.7% (23/75) for the historical control group ($p < 0.0001$; Chi-square test). Post-hoc analysis showed that 91% (88/97) of evaluable RBX2660 responders remained CDI occurrence-free to 24 months after treatment showing durability. RBX2660 was well-tolerated with primarily mild to moderate adverse events. Limitations to the study were the open-label design and exclusion of individuals with specific comorbidities common to the rCDI population, i.e., inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). The authors concluded that FMT using RBX2660 was safe and effective for reducing rCDI compared to a historical control group.

In a 2021 randomized clinical trial (RCT), authors Rode et al. aimed to compare the efficacy of a 12-strain mixture termed rectal bacteriotherapy with either FMT or vancomycin for rCDI before FMT and rectal bacteriotherapy; participants were pre-treated with vancomycin for 7-14 days. Rectal bacteriotherapy was applied by enema on three consecutive days and FMT by enema once with repetition for two to three infusions within 14 days. The vancomycin group was treated for 14 days with added five weeks of tapering for multiple recurrences. The primary outcome was a clinical cure within 90 days, with the secondary outcome being 180 day all-cause mortality. The results showed that participants in the FMT group (n = 34) were cured more often than participants receiving vancomycin (n = 31), 76% vs. 45% [OR 3.9 (1.4-11.4), $p < 0.01$] or rectal bacteriotherapy (n = 31), 76% vs. 52% [OR 3.0 (1.1-8.8), $p = 0.04$]. Rectal bacteriotherapy and vancomycin were performed similarly ($p = 0.61$). The mortality rate was 6% in the FMT group, 13% in the bacteriotherapy group, and 23% in the vancomycin group. FMT tended to reduce mortality compared with vancomycin, [OR 0.2 (0.04-1.12), $p = 0.07$]. The authors concluded that rectal bacteriotherapy appears as effective as vancomycin but less effective than 1-3 FMTs. FMT by an enema with 1-3 infusions is superior to vancomycin for treating rCDI and might reduce mortality.

In 2021 Ramai and associates systematically reviewed a meta-analysis of four different methods of FMT administration [colonoscopy, capsule, enema, and nasogastric tube (NGT)] for treating rCDI. The clinical outcomes were assessed, with the primary outcome measure being the overall cure rate assessed using a random effects model. The secondary outcomes included adverse effects, subgroup analyses comparing donor relationships, sample preparation, and study design. Included in the study were 26 articles (1,309 individuals), with FMT being administered via colonoscopy in 16 studies (483 individuals), NGT in five studies (149 individuals), enema in four studies (360 individuals), and four studies using capsules (301 individuals). The exploration resulted in the random effects of pooled FMT cure rates as follows: colonoscopy 94.8% (CI 92.4-96.8%; I2 15.6%), capsule 92.1% (CI 88.6-95.0%; I2 7.1%), enema 87.2% (CI 83.4-90.5%; I2 0%), and NGT/NDT 78.1% (CI 71.6-84.1%; I2 0%). A significant limitation of the systematic review and meta-analysis is that most studies used colonoscopy as their FMT administration, leaving little data on NGT, enema, and capsules. The authors concluded in this meta-analysis that FMT was well tolerated in the management of rCDI.

In a 2020 systematic review and meta-analysis, Baunwall et al. sought to uncover the current evidence of FMT for rCDI across different delivery methods (lower gastrointestinal endoscopy, endoscopy, upper gastrointestinal administration, capsules, and enema) and treatment regimens and compare it with standard antibiotics. The primary outcome measure was clinical outcome

by week eight after comprehensively extracting individual and procedural data. By way of random-effects meta-analysis, the authors estimated the clinical effect of repeat or single FMT and various delivery methods versus antibiotics. The exploration uncovered 45 studies. The overall clinical development on week eight following repeat FMT included 24 studies, 1,855 participants (91%) with 95% CI: 8994%, I^2 = 53%. The single FMT included 43 studies, 2,937 participants (84%) 8,088%, I^2 = 86%. The gastrointestinal endoscopy was superior to all other delivery methods and repeat FMT significantly increased the treatment effect at week 8 (< 0.001); however, the highest absolute increase in treatment effect was observed for enema FMT that increased from 50% (45-55%, I^2 = 0%) following single FMT to 88% (83-93%, I^2 = 37%) for repeat FMT (p < 0·001). The number needed to treat (NNT) for repeat FMT compared with vancomycin was 1.5 (1.3-1.9, p < 0.001) and 2.9 (1.5-37.1, p = 0.03) for single FMT. The lack of included participants with refractory index CDI limits this review. Future research may determine how FMT performs without antibiotic pre-treatment and how it measures in individuals with initial CDI. The authors concluded that there is existing high-quality evidence that supports FMT as an effective treatment for rCDI, depending on the delivery method and number of administrations. The superior NNT for FMT, as compared with antibiotics, suggests that individuals may profit from advancing FMT to all occurrences of rCDI (Included in ECRI., 2018).

In 2019, a RCT meta-analysis by Hui et al. focused on fresh FMT and fecal infusion times to guide clinical practice. The authors separated individuals into groups; fresh FMT, and a control group consisting of antibiotic therapy, placebo, frozen FMT, or capsule FMT administration. Clinical remission of diarrhea without relapse after 8-17 weeks was the primary outcome measure, and the secondary measure was the occurrence of severe adverse events. After the inclusion of eight RCTs, 537 individuals were included in the analyses (273 in the fresh FMT group and 264 in the control group). The evaluation uncovered a recurrence rate of clinical diarrhea in the fresh FMT group of 11% (30/273) and 24.6%, (65/264) resulting in the FMT group's recurrence being significantly lower than the control group; p < 0.05. The pooled relative risk was 0.38 (95% CI:0.16-0.87; I^2 = 67%; p = 0.02) for the fresh FMT group and using the random effects model, the clinical heterogeneity was significant. The results of the antibiotic treatment/frozen feces transplanted by enema were recurrence rate = 1.07; 95% CI: 0.64-1.80; I^2 = 0%; p = 0.79, and capsule/frozen feces transplanted by colonoscopy RR = 0.42; 95% CI: 0.05-3.94; I^2 = 43%; p = 0.45, which is no significant difference when compared to fresh FMT. The study was limited by its small sample size and lack of fresh donor stool. The authors concluded that using fresh feces for bacterial transplantation has the best efficiency for rCDI when compared to antibiotic therapy or placebo.

The results from a randomized, double-blinded, placebo-controlled phase 2B Clinical Trial of RBX2660 were conveyed by Dubberke et al. in 2018. The trial registered adults 18 years or older with two or more CDI recurrences. The contributors were randomized to three groups; group A who received two doses of RBX2660, a standardized microbiota-based drug, group B who received two doses of placebo), and group C who received one dose of RBX2660 followed by one dose of placebo. To be considered adequate, RBX2660 must show prevention of rCDI at eight weeks following treatment. Individuals experiencing recurrence within the eight weeks of treatment could receive up to two open-label RBX2660 doses. Group A and Group B's efficacy were compared as the primary endpoint; secondary endpoints were the efficacy of group C compared to group B, collective efficacy in the blinded and open-label phases, and safety for 24 months. The trial results for effectiveness showed group A (61%), group B (45%), and group C (67%). The primary endpoint of efficacy for group A compared to group B was not met (p = .152). Group C, who received one RBX2660 dose, was superior to group B with the placebo; p = .048, with the overall efficacy including open-label response for RBX2660, treated participants resulting in 88.8%. Treatment group adverse events did not differ significantly. The authors concluded that the trial adds substantial long-term safety data for microbiota-based rCDI therapies as the overall safety profile was favorable at the average follow-up of 8.3 months and underscores the safety of enema administration. The authors concluded that RBX2660 was safe and well tolerated.

In a 2018 single-center RCT, Jiang et al. aimed to compare the safety and preliminary efficacy of orally administered lyophilized microbiota with a frozen product by enema. A total of 65 adults, non-pregnant, who had greater than three total episodes of CDI and received at least one course of anti-CDI antibiotics for the most recent bout met inclusion criteria and were randomized 1:1 to receive encapsulated lyophilized fecal microbiota from 100-200 g of donor feces (n = 31) or frozen FMT from 100 g of donor feces (n = 34) by enema. For three months post-FMT, the primary outcome was safety; for 60 days following FMT, the secondary outcome was the prevention of CDI recurrence. The trial prevented CDI recurrence in 84% (26 of 31 participants) randomized to capsules and 88% (30 of 34 participants) of those receiving FMT by enema. A higher number of individuals in the oral group experienced nausea or fecal urgency; in the enema group, more participants experienced abdominal cramping. The trial was limited by the short-term follow-up, self-reported adverse events, inability to compare the efficiency of more than one oral dose as there was a small sample size, and inability to perform spore counts. Although long-term randomized control trials with large populations can validate the study's outcomes, the authors concluded that both routes appeared to show equivalent efficacy (included in the 2020 Baunwall systematic review).

Orenstein et al. aimed to assess the safety and effectiveness of RBX2660 (microbiota suspension) administered via enema in 2016, through the results of a prospective, multicenter open-label study (PUNCH CD). Adults with at least two rCDI episodes or at least two severe episodes resulting in hospitalization were enrolled and totaled 40 participants at 11 centers. Adverse events were monitored after treatment for seven, 30, 60, 90, and 180 days with the primary objective being product-related adverse events and the secondary objective CDI-associated diarrhea resolution at eight weeks. The results at six months follow-ups were an overall efficacy of 87.1%, with diarrhea, flatulence, abdominal pain/cramping, and constipation being the most reported adverse event, although the frequency and severity of adverse events decreased over time. The study is limited by the lack of a control arm, a small sample size, and limited follow-up (6 months). The authors concluded that RBX2660 demonstrated a good safety profile for rCDI, and administration via enema can decrease risks compared with a nasoduodenal tube or colonoscopic administration (included in the 2020 Baunwall systematic review, and 2021 Ramai systematic review and meta-analysis).

FMT for Treating Crohn's Disease (CD)

There is insufficient evidence for the efficacy of treating CD with FMT. FMT is unproven and not medically necessary for prevention and/or treatment of CD.

In 2023, Zhou and colleagues performed a systematic review and meta-analysis to evaluate the efficacy and safety of FMT for CD. The primary outcome measured was clinical remission, with the clinical response, endoscopic remission, minor adverse events, serious adverse events, and changes in disease activity indices, biochemical indicators, and microbial diversities being the secondary outcomes measured. The review resulted in eleven cohort studies and one RCT involving 228 individuals. In a meta-analysis, the pooled proportion of adults with active CD that achieved clinical remission two to four weeks after FMT was 57% (95% CI = 49-64%) with a low risk of heterogeneity (I2 = 37%). Furthermore, our results showed that FMT significantly (standardized mean difference = -0.66; 95% CI = -1.12 to -0.20; I2 = 0) reduced Crohn's disease activity index scores 4 to 8 weeks after FMT. Subgroup analyses showed no difference between FMT methodologies, except for pre-FMT treatment with antibiotics (p = 0.02). Most adverse events were self-limiting and disappeared spontaneously within hours or days after FMT. Microbiota analysis showed an increased Shannon diversity and a shift toward a donor-like microbiome after FMT. The authors concluded that FMT could be a promising therapy in the short-term treatment of active CD. However, more placebo-controlled randomized trials with a long-term follow-up treatment are necessary.

In 2022, Hayes developed a health technology assessment on FMT for treating CD in adults and pediatric individuals that have not sufficiently responded to medical management. The evaluation focused on the safety and efficacy of FMT for CD which uncovered a deficiency of quality evidence to conclude the efficacy of FMT to aid individuals with CD in attaining or maintaining remission. The assessment discovered that the procedure is safe in the adult and pediatric population. Considerable ambiguity remains on the degree of the benefits, which individuals might profit from the treatment, ideal treatment parameters, and whether there is a long-term benefit. Based on a review of abstracts for the 2023 update, there is one newly published study that may meet the inclusion criteria set out in the report. The update yielded no change in current rating of D2.

In a 2021 systematic review and meta-analysis, Cheng et al. evaluated the safety and efficacy of FMT for individuals with CD. Included in the study were 12 trials overall. The primary outcome measure was clinical remission, and the secondary outcome was the clinical response. The results of the review uncovered a pooled analysis showing that 0.62 (95% CI 0.48, 0.81) of individuals with CD attained clinical remission, and 0.79 (95% CI 0.71, 0.89) of individuals with CD reached clinical response post-FMT. Sub-analyses proposed that the rate of clinical remission with fresh stool FMT was higher than with frozen stool FMT (73% vs. 43%; $p < 0.05$). Most adverse events were minor and self-resolving, and no major FMT-related adverse events were reported. Limitations of the review include a small sample size, the need for a control arm, and short-term follow-up. The authors concluded that FMT is an effective and safe therapy for CD; however, additional randomized controlled studies are needed for verification (included in Hayes, 2022).

Through a systematic review in 2021, Fehily and colleagues evaluated the efficacy of FMT for CD. The exploration uncovered 15 studies, with the majority considering FMT for remission induction, with a follow-up duration between 4 to 52 weeks. The primary outcome measured was clinical outcomes. One RCT evaluated, including 21 individuals who received single dose FMT vs. placebo following steroid-induced remission, showed a higher rate of steroid-free clinical remission in the FMT group equated to the control group: 87.5% vs. 44.4% at week 10 (p = 0.23). Another RCT, two-dose FMT in 31 individuals, displayed a total clinical remission rate of 36% at week 8, with no difference in clinical or endoscopic endpoints amongst FMT administered by gastroscopy and colonoscopy. With all studies, the clinical response rates in immediate follow-up were better after several FMT administrations than with a single FMT administration. FMT dose did not change clinical results, nor if FMT was frozen or

fresh. FMT distributed via the upper gastrointestinal route offered higher initial effectiveness rates of 75% to 100%, equated with lesser delivery route rates of 30% to 58%; nonetheless, this variance was not upheld on follow up past eight weeks. The benefit of pre-FMT antibiotic administration still needs to be determined due to the limited number of participants receiving antibiotics and fluctuating antibiotic regimens. No serious adverse events were reported. The authors concluded that the studies propose that FMT may be an effective therapy in CD; nevertheless, large, controlled trials are required to corroborate that conclusion (included in Hayes, 2022).

In a prospective, open-label, single-center study, Gutin and associates (2019) aimed to determine if the single-dose FMT improves clinical and endoscopic outcomes for individuals with CD while identifying meaningful changes in the microbiome in response to FMT. The primary outcome was the clinical response which was assessed with the Harvey-Bradshaw Index score (≥ 3 at one month following FMT) and microbiome profile (16S ribosomal RNA sequencing at one month following FMT). Included in the study were ten individuals who underwent FMT and were evaluated for clinical response. The results showed that three of the ten individuals responded to FMT, two had significant adverse events requiring an escalation of therapy, and bacterial communities of responders had increased relative abundance of bacteria commonly found in donor gut microbiota on the microbiome analysis. The study is limited by the open-label design, lack of a control arm, and small sample size. The authors concluded that single-dose FMT in this cohort of individuals with CD exhibited modest outcomes and potential for harm. Respondents were inclined to have lower baseline alpha diversity, signifying that baseline microbiota perturbation may indicate possible responders to FMT in this population. Controlled trials are required to further assess the safety and efficacy of FMT for CD and study if FMT is a feasible option in this population (included in the 2021 Cheng systematic review, and the 2023 systematic review and meta-analysis by Zhou et al.).

In a Cochrane review, Imdad and colleagues (2018) explored the safety and efficacy of FMT for treating IBD. The authors studied RCTs or non-RCTs with a control arm, including adults or children with UC or CD who received FMT, and the comparison group who did not. The primary outcomes were the introduction of clinical remission, clinical relapse, and serious adverse events. Secondary outcomes encompassed clinical response, endoscopic remission, endoscopic response, quality of life scores, laboratory measures of inflammation, withdrawals, and microbiome results. Overall, 277 participants were included in the investigation. Joint outcomes from four studies (277 participants) propose that FMT increases rates of clinical remission by two-fold for individuals with UC versus controls. At eight weeks, 37% (52/140) of FMT participants attained remission versus 18% (24/137) of control participants (RR 2.03, 95% CI, 1.07 to 3.86; IO = 50%; low certainty evidence). At 12 weeks, none of the FMT participants (0/7) relapsed versus 20% of control participants (RR 0.28, 95% CI 0.02 to 4.98, 17 participants, deficient certainty evidence). The authors concluded that FMT might increase the number of participants accomplishing clinical remission in UC. The number of uncovered studies was small, and the quality of evidence needed to be higher. There are reservations about the rate of serious adverse events; consequently, no solid conclusions can be drawn now. More high-quality studies are required to further define the optimal parameters of FMT in terms of route, frequency, volume, preparation, type of donor, and the type and disease severity.

FMT for Treating Ulcerative Colitis (UC)

There is insufficient evidence for the efficacy of treating UC with FMT. FMT is unproven and not medically necessary for prevention and/or treatment of UC.

In 2023, Lahtinen and associates investigated FMT for the maintenance of remission for individuals with UC through an RCT. For the investigation, 48 individuals with UC were randomized to receive a single-dose FMT or autologous transplant via colonoscopy. The primary endpoint was the maintenance of remission, a fecal calprotectin level below 200 μg/g, and a clinical Mayo score below three throughout the 12-month follow-up. The person's quality of life, fecal calprotectin, blood chemistry, and endoscopic findings were recorded as secondary endpoints at 12 mo. The trial results showed that the primary endpoint was achieved by 13 out of 24 people (54%) in the FMT group and by 10 out of 24 people (41%) in the placebo group (log-rank test, p = 0.660). Four months after FMT, the quality-of-life scores decreased in the FMT group compared to the placebo group (p = 0.017). In addition, the disease-specific quality of life measure was higher in the placebo group than in the FMT group at the same time (p = 0.003). There were no differences in blood chemistry, fecal calprotectin, or endoscopic findings among the study groups at 12 months. The adverse events were infrequent, mild, and distributed equally between the groups. The authors concluded no differences in the number of relapses between the study groups at the 12-month follow-up. The results do not support the use of a single-dose FMT for the maintenance of remission in UC (included in the 2021 Hayes, 2023 update).

Through a systematic review and meta-analysis of double-blind, RCTs, El Hage Chehade et al. (2023) sought to evaluate the benefit of FMT for individuals with UC. Inclusion criteria consisted of double-blind, RCTs that included adult individuals with

active UC who received FMT or placebo. The outcomes measured were the rate of combined clinical and endoscopic remission, endoscopic remission or response, clinical remission or response, and specific adverse events. The results of this review uncovered that six RCTs involving 324 participants were included. The findings demonstrate that compared with placebo, FMT significantly benefits in inducing combined clinical and endoscopic remission (odds ratio, 4.11; 95% confidence interval, 2.19-7.72; p < .0001). Subgroup analyses of influencing factors showed no differences between pooled or single stool donors (p = .71), fresh or frozen FMT (p = .35), and different routes or frequencies of delivery (p = .80 and .48, respectively). Pre-FMT antibiotics, bowel lavage, concomitant biologic therapy, and topical rectal therapy did not affect combined remission rates (p values of .47, .38, .28, and .40, respectively). Clinical remission or response and endoscopic remission or response were significantly higher in those who received FMT than placebo (p < .05) without any differences in severe or specific adverse events. The authors concluded that FMT demonstrated a clinical and endoscopic benefit in the short-term treatment of active UC, with a comparable safety profile to placebo; however, future RCTs are required to standardize study protocols and examine data on maintenance therapy.

In 2023, Feng et al. conducted a systematic review and meta-analysis to investigate the efficacy and safety of FMT for treating UC. A total of 13 RCTs on the efficacy of FMT for individuals with UC were included in the study, in which 580 participated, including 293 that were treated with FMT and 287 control subjects. The meta-analysis revealed that clinical remission was significantly better in the FMT group than in the control group [RR = 1.73; 95% CI = (1.41, 2.12); p < 0.00001]; endoscopic remission was significantly better in the FMT group than in the control group [RR = 1.74; 95% CI = (1.24, 2.44); p = 0.001]. There were no significant differences in the incidence of adverse reactions between the two groups [RR = 1.00; 95% CI = (0.86, 1.15); p = 0.96]. A limitation of the study includes the evaluation time needed to be more consistent and the distinction of individual types required to be clarified across studies. The authors concluded that FMT has shown potential as a therapeutic intervention for inducing clinical remission in UC; nevertheless, the attainment of endoscopic remission and the maintenance of long-term remission continue to present challenges. Safety concerns persist throughout treatment, needing measures to augment safety and success rates.

In 2021, Hayes conducted a Health Technology Assessment for the use of FMT to treat adults with UC that has not adequately responded to medical management. The assessment appoints FMT as a conventional treatment for individuals with rCDI. Its role as a possible treatment to help individuals with UC accomplish remission remains to be determined, chiefly due to an absence of standardized FMT protocols and immense heterogeneity in study design. A low-quality body of evidence proposes that donor FMT (dFMT) may result in clinical remission, clinical response, and reduced disease severity in some individuals with UC that has not responded sufficiently to regular medical care. The use of dFMT is safe, with usually mild and transient complications, among the RCTs comparing dFMT with placebo or autologous FMT (aFMT) in individuals with UC. Considerable ambiguity remains due to irregularities in results across studies and heterogeneity in treatment protocols. Based on a review of abstracts, in the 2023 update there are nine newly published studies that may meet the inclusion criteria set out in the report, which was published in 2021. The 2023 update required no change in current rating of C.

In 2022, Huang and associates conducted a systematic review with a meta-analysis of FMT for treating UC to assess the efficiency and safety due to FMT's promising yet controversial therapy for UC. The systematic review consisted of 34 articles, the meta-analysis 16 articles, including 4 RCTs, two controlled clinical trials, and 10 cohort studies. The study led to finding the donor FMT more effective than the placebo for achieving total remission with results as follows: RR 2.77, 95% CI 1.54-4.98; p = .0007), clinical remission (RR: 0.33, 95% CI: 0.24-0.41; p < .05), and steroid-free remission (RR: 3.63, 95% CI: 1.57-8.42; p = .003). There was no statistically significant difference in the incidence of serious adverse events (RR: 0.88, 95% CI: 0.34-2.31, p = .8), and in the subgroup analysis, there were significant differences between the pooled clinical remission rates for different regions, degrees of severity of the disease, and individuals with steroid or non-steroid dependent UC. Limitations to the study include small sample size and bias risk, and the subgroup analysis is only performed on populations and outcomes. The authors concluded that FMT can achieve clinical remission and may achieve steroid-free remission for individuals with UC; however, more extensive studies and clinical trials that report these factors are urgently needed to determine the best conditions for FMT.

Liu and colleagues (2021) noted that although FMT is an effective treatment against rCDI, its efficiency in treating UC is still controversial. In a systematic review and meta-analysis, these researchers studied the safety and efficacy of FMT for treating active UC. The primary outcome was collective clinical remission with endoscopic remission/response, and the secondary outcome was clinical remission, endoscopic remission, and serious adverse events. The review exposed five RCTs comprising of 292 individuals. The results of the pooled data showed FMT had a higher mutual clinical remission with endoscopic remission/response, and the RR of combined outcome not achieving after FMT versus control was 0.79 (95% CI: 0.70 to 0.88)

for all individuals. FMT distributed by the lower GI route was more significant than the upper GI route regarding combined clinical remission with endoscopic remission/response (RR = 0.79, 95% CI: 0.70 to 0.89). FMT with pooled donor stool (RR = 0.69, 95% CI: 0.56 to 0.85) and higher incidence of administration (RR = 0.76, 95% CI: 0.62 to 0.93) might be more effective regarding clinical remission. Serious adverse events with FMT compared with controls showed no statistically significant difference (RR = 0.98, 95% CI: 0.93 to 1.03). The authors concluded that FMT exhibited a hopeful outlook with similar safety and good clinical efficacy for treating active UC in the short term. Future, more extensive, more rigorous RCTs must still address controversial queries concerning donor selection, treatment before FMT, ideal stool or microbiota dosage, the occurrence of administration, predictors of individuals most likely to respond, the most effective distribution route in different circumstances, and cost-effectiveness.

In a systematic review with meta-analysis, Dang and colleagues (2020) compared the safety and efficacy of primary treatment combined with FMT or mixed probiotics therapy in relieving mild-to-moderate UC. Seven randomized, double-blind, placebo-controlled trials were used as the source's information. The outcome measures were adverse events, severe events, clinical remission, and clinical response. The results of the exploration uncovered that all treatments were superior to placebo. Regarding clinical remission and clinical response to active UC, direct comparisons displayed FMT (OR = 3.47, 95% CI: 1.93 to 6.25) (OR = 2.48, 95% CI: 1.18 to 5.21) and mixed probiotics VSL#3 (OR = 2.40, 95% CI: 1.49 to 3.88) (OR = 3.09, 95% CI: 1.53 to 6.25) to have better effects than the placebo. Indirect comparison displayed FMT, and probiotic VSL#3 was unable to reach statistical significance for clinical remission (RR = 1.20, 95% CI: 0.70 to 2.06) or clinical response (RR = 0.95, 95% CI: 0.62 to 1.45). Regarding safety, FMT (OR = 1.15, 95% CI: 0.51 to 2.61) and VSL#3 (OR = 0.90, 95% CI: 0.33 to 2.49) presented no statistically significant rise in adverse events versus the control group. There was no statistical variance for severe adverse events between the FMT group and the control group (OR = 1.29, 95% CI: 0.46 to 3.57). The probiotics VSL#3 looked safer than FMT since SAEs were not reported in the VSL#3 articles. The authors concluded that although FMT or mixed probiotics VSL#3 accomplished good outcomes in clinical remission and clinical response in active UC, and there was no increased risk of AEs, the use of FMT and probiotics still has many unresolved issues in clinical applications. More RCTs are required to confirm FMT's efficacy for UC.

Narula and colleagues (2017) performed a systematic review and meta-analysis to evaluate FMT as a treatment for active UC. The primary outcome was combined clinical remission and endoscopic remission or response, with secondary outcomes, including clinical remission, endoscopic remission, serious adverse events, and OR with 95% CIs. In total, four studies with 277 individuals were included in the investigation. The review uncovered that FMT was associated with higher joint clinical and endoscopic remission versus placebo [risk ratio (RR) UC not in remission was 0.80; 95% CI: 0.71 to 0.89] with an amount required to treat of 5 (95% CI: 4 to 10). Compared to controls, there was no statistically significant increase in SAEs with FMT (RR for AE was 1.4; 95% CI: 0.55 to 3.58). The authors concluded that across the RCTs, short-term use of FMT exhibited the potential to induce remission in active UC based on the observed safety and efficacy. There continue to be many unanswered queries that necessitate further research before FMT can be considered for use in clinical practice. Currently, there is no long-term safety data for FMT in UC, there is uncertainty about the most effective delivery modality of FMT, the ideal dosage for both induction and the maintenance doses is not yet defined, and the impact of the donor is unknown.

FMT for Treating Irritable Bowel Syndrome (IBS)

There is insufficient evidence for the efficacy of treating IBS with FMT. FMT is unproven and not medically necessary for prevention and/or treatment of IBS.

In 2023, Rokkas & Hold updated a systematic review, and pairwise network meta-analyses published in the past and assessed the comparative efficacy and safety of various FMT delivery modalities for IBS. The exploration results showed that of 510 titles raised by the initial search, seven RCTs were entered into meta-analyses and NWM. They included 470 individuals and controls, in whom four FMT delivery modalities were used: colonoscopy, naso-jejunal tube, duodenoscope, and capsules per os. In the pairwise meta-analysis, the pooled results showed that overall FMT was not superior to placebo, while the subgroup analyses showed that FMT via duodenoscope and naso-jejunal tube was superior. The NWM showed that 60-g FMT via duodenoscope had the highest efficacy (OR, 26.38; 95% CI, 9.22-75.51) and was the highest in the efficacy ranking (SUCRA, 98.8%). The authors concluded that there is no overall advantage of FMT over placebo in IBS. However, upper GI delivery (via duodenoscopy or naso-jejunal tube) proved effective. Consequently, well-designed RCTs are needed to ensure the efficacy and safety profile before FMT can be applied in everyday clinical practice for individuals with IBS.

Through a systematic review and meta-analysis of RCTs, Jamshidi et al. (2023) sought to validate the efficacy of FMT for relieving symptoms of IBS. The effectiveness of FMT for reducing symptoms overall and subgroups classified by placebo

preparation, FMT preparation, frequency, and route of administration was examined. The results of this exploration showed that the overall symptomatology of FMT-treated individuals with IBS did not significantly differ from the control group [Odds Ratio (OR) = 0.99, 95% Confidence Interval (CI) 0.39-2.5]. Multiple doses of FMT compared with non-FMT placebo or single-donor FMT therapy compared with autologous FMT placebo also showed no significant benefit [OR = 0.32, 95% CI (0.07-1.32), p = 0.11, and OR = 1.67, 95% CI (0.59-4.67), p = 0.32, respectively]. However, a single dose of multiple-donor FMT administered via colonoscopy [lower gastrointestinal (GI) administration] significantly improved symptoms compared with autologous FMT placebo [OR = 2.54, 95% CI (1.20-5.37), p = 0.01, and OR = 2.2, 95% CI (1.20-4.03), p = 0.01, respectively]. The studies included in the analysis showed a low risk of bias and no publication bias. The authors concluded that the lower GI administration of a single dose of multiple-donor FMT significantly alleviates complaints compared with the autologous FMT used as a placebo. The underlying mechanisms need to be better understood, and further experimental studies are desired to fill the current gaps.

Wang et al. (2023) sought to determine whether FMT for individuals with IBS is effective for improving outcomes through a systematic review and meta-analysis of RCTs. The trials included comparing the stool and capsule FMT with a placebo for individuals with IBS. The primary outcomes measured were the clinical response rate and IBS-SSS scores. This exploration found that nineteen reports from nine RCTs were finally included. Compared with the placebo, a single stool FMT could significantly decrease the IBS-SSS score at one month [MD = -65.75, 95% CI (-129.37, -2.13)], three months [MD = -102.11, 95% CI (-141.98, -62.24)], six months [MD = -84.38, 95% CI (-158.79, -9.97)], 24 months [MD = -110.41, 95% CI (-145.37, -75.46)], and 36 months [MD = -104.71, 95% CI (-137.78, -71.64)]. It also could improve the clinical response rate at three months [RR = 1.91, 95% (1.12, 3.25)], 24 months [RR = 2.97, 95% (1.94, 4.54)], and 36 months [RR = 2.48, 95% (1.65, 3.72)], and increase the IBS-QoL score at three months, 24 months, and 36 months. FMT did not increase the serious adverse event. The risk of bias was low, and the quality of evidence based on the GRADE system was moderate in the stool FMT group. However, based on the currently available data, we did not find a positive effect of capsule FMT on individuals with IBS. The authors concluded that a single stool FMT is effective and safe for those with IBS. However, some factors may affect the effectiveness of FMT, and the relationship between the gut microbiome and the effect of FMT on IBS is still unclear.

Halkjær and associates (2023) assessed the efficacy and safety of FMT for treating IBS through a systematic review and meta-analysis. Included in the investigation was an RCT that explored the effectiveness of FMT compared to placebo in treating IBS. The outcomes measured were the number of individuals who demonstrated improvements in their symptoms using validated global IBS symptoms score, changes in quality-of-life scores, and severe and non-serious adverse events. Eight RCTs (484 participants) were included in the review. FMT resulted in no significant benefit in IBS symptoms three months after treatment compared to placebo (RR 1.19, 95% CI: 0.68-2.10). Adverse events were reported in 97 participants in the FMT group and 45 in the placebo group (RR 1.17, 95% CI: 0.63-2.15). One serious adverse event occurred in the FMT group and two in the placebo group (RR 0.42, 95% CI: 0.07-2.60). Endoscopic FMT delivery resulted in a significant improvement in symptoms, while capsules did not. FMT did not improve the quality of life of individuals with IBS but appeared to reduce it, albeit not significantly (MD -6.30, 95% CI: -13.39-0.79). The overall quality of the evidence was low due to moderate-high inconsistency, the small number of study participants, and imprecision. The authors concluded that insufficient evidence supports or refutes the use of FMT for IBS. More extensive trials are needed.

ECRI developed a Clinical Evidence Assessment reporting on FMT for treating IBS, focusing on FMT's safety and effectiveness. The assessment concluded that FMT has not consistently improved IBS symptoms across studies (ECRI 2018; updated 2022).

Through a single-center RCT, Tkach and colleagues (2022) assessed FMT's safety and clinical and microbiological efficacy for individuals with post-infectious irritable bowel syndrome (PI-IBS). Participants were randomized to either the standard care group (n = 29), where they were prescribed basic therapy consisting primarily of a low FODMAP diet, Otilonium Bromide (1-tab TID), and a muti-strain probiotic (1 capsule BID) for one month, or the FMT group (n = 30) where each participant with PI-IBS undertook a single FMT procedure with fresh material by colonoscopy. Bacteriological examination of feces for quantitative and qualitative microbiota composition changes took place for all participants, and the clinical efficacy was evaluated according to the dynamics of abdominal symptoms. The clinical effectiveness of treatment was measured using the IBS-SSS scale, fatigue reduction (FAS scale), and a change in the quality of life (IBS-QoL scale). The trial resulted in FMT being related to a fast onset of the effect established in a significant difference between IBS-SSS points following two weeks of intervention ($p < 0.001$). Following 4 and 12 weeks, IBS-SSS did not vary meaningfully across both groups. After three months of treatment, the QoL surpassed its initial level and value for 2 and 4 weeks to a considerable degree. No severe adverse reactions were recorded. The study limitations include the absence of blinding and the small sample size. The authors concluded that even a single administration significantly affects the IM by reducing the frequency and severity of dysbiotic disorders, accompanied by

significant clinical improvement in most individuals up to three months, comparable to pharmacotherapeutic methods. Nonetheless, there remain several uncertainties related to the effectiveness of FMT.

Wu et al. (2022) examined RCTs regarding the efficacy of FMT in IBS in a meta-analysis assessing both the short- and long-term effectiveness. The investigation generated 658 citations: seven RCTs comprising 472 individuals with IBS. The results uncovered that FMT was not related to a noteworthy improvement in overall symptoms in IBS at 12 weeks in contrast to placebo (RR 0.75, 95% CI: 0.43 to 1.31) with high heterogeneity amongst articles (I2 87%). Subgroup analyses displayed FMT as superior to placebo when administered through colonoscopy or gastroscope (RR 0.70, 95% CI: 0.51 to 0.96; RR 0.37, 95% CI: 0.14 to 0.99), respectively, while FMT was inferior to placebo when administered via oral capsules (RR 1.88, 95% CI: 1.06 to 3.35). FMT stimulated a significant enhancement in IBS-QOL associated with placebo (MD 9.39, 95% CI: 3.86 to 14.91) at 12 weeks. There was no considerable variance in the overall number of AEs amongst FMT and placebo (RR 1.20, 95% CI: 0.59 to 2.47). FMT did not meaningfully advance universal symptoms in IBS at 1-year follow-up versus with placebo (RR 0.90, 95% CI: 0.72 to 1.12). The GRADE quality evidence to sustenance endorsing FMT in IBS needed to be revised. Limitations of the study included no reflection of the actual dose-response effect of FMT and the presence of heterogeneity. The authors concluded that individuals with IBS may profit from FMT when administered via colonoscopy or gastroscope; FMT may improve individuals' QOL. The long-term use of FMT in IBS permits further examination; very low-quality evidence supports endorsing FMT for IBS (included in the 2022 update of ECRI, 2018).

Holvoet et al. (2021) conducted a randomized placebo-controlled trial to appraise the effectiveness of FMT for individuals with predominant abdominal bloating due to IBS. Individuals with refractory IBS (defined as having a failure of more than three conventional therapies) were randomly assigned 2:1 to two groups. Group one received a single dose nasojejunal administration of donor stools (n = 43), and group two had autologous stools (n = 19, placebo). A daily symptom diary was utilized to assess IBS-related symptoms determining general abdominal discomfort, abdominal bloating, pain, and flatulence on a scale of 1-6, along with several daily bowel movements, stool consistency, and abdominal circumference. Primary endpoints were improvement of IBS symptoms and bloating at 12 weeks (response), with secondary endpoints being changes in IBS symptom scores and quality of life. Quality of life was assessed using the completed IBS-specific quality of life questionnaire. Follow-up occurred through one year, and the results at 12 weeks showed improvement in both primary endpoints was reported in 56% of the treatment group versus 26% in the placebo group (p = 0.03). The treatment group described progress in the level of discomfort with a mean reduction of 19%, stool frequency with a mean decrease of 13%, urgency with a mean decrease of 38%, abdominal pain with a mean reduction of 26%, flatulence with a mean decrease of 10%, and quality of life with a mean increase of 16%. At one year, 21% of the treatment group reported long-term effects versus 5% of the placebo group. The use of outdated selection criteria (ROME III) limits the study. The authors concluded that single transplantation of fresh donor stools by nasojejunal administration could relieve abdominal symptoms for individuals with refractory IBS and severe abdominal bloating. Although the results of this trial are positive, utilizing FMT for individuals with IBS does not guarantee success, is subtype-dependent, and is limited in time (included in the 2023 Jamshidi systematic review and meta-analysis, and the 2023 Rokkas & Hold systematic review).

Through a systematic review and meta-analysis, Myneedu and colleagues (2019) examined if FMT successfully treats IBS. Ratios and RR of improvement for single-arm trials (SATs) and RCTs were calculated, respectively. Changes in the IBS Severity Scoring System (IBS-SSS) and IBS Quality of Life (IBS-QOL) instrument compared to baseline in FMT against placebo groups were pooled. In SATs, 59.5% (95% CI: 49.1 to 69.3) of individuals with IBS displayed noteworthy improvement. There were no differences between FMT and control in advance [RR = 0.93 (95% CI: 0.50 to 1.75)] or changes in the IBS-SSS and IBS-QOL in RCTs. The authors concluded that FMT was not a successful treatment strategy for individuals with IBS.

In a systematic review and meta-analyses of available RCTs, Xu and associates (2019) appraised the efficacy of FMT for IBS. Meta-analyses were conducted to gauge the summary RR and 95% CIs of shared studies for the prime outcome of improvement in international IBS symptoms measured by accepted integrative symptom questionnaires or dichotomous replies to questions of total symptom enhancement. In total, four studies involving 254 participants were included in the review. The results of the review demonstrated no significant difference in the global improvement of IBS symptoms versus placebo (RR = 0.93; 95% CI: 0.48 to 1.79), and heterogeneity among studies was significant (I = 79%). Subgroup analyses revealed benefits of single-dose FMT using colonoscopy and nasojejunal tubes in contrast to autologous FMT for placebo treatment (number needed to treat = 5, RR = 1.59; 95% CI: 1.06 to 2.39; I = 0%) and a decrease in the probability of improvement of multiple-dose capsule FMT RCTs (number needed to harm = 3, RR = 0.54; 95% CI: 0.34 to 0.85; I = 13%). Placebo response was 33.7% and 67.8% in non-oral and capsule FMT RCTs, respectively. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) quality of the body of evidence needed to be improved, and the authors concluded that existing evidence

from RCTs does not acclaim a benefit of FMT for global IBS symptoms. There remain inquiries concerning the effectiveness of FMT in IBS and the absence of a clear description of the incompatible outcomes among RCTs in subgroup analyses.

Ianiro and associates (2019) completed a systematic review and meta-analysis to study the efficacy of FMT for IBS. The exploration uncovered 322 citations: five RCTs containing 267 individuals. In total, 92.2% of involved individuals had IBS with diarrhea (IBS-D) or IBS with mixed stool pattern (IBS-M), and 7.8% had IBS with constipation (IBS-C). The results of the pooled data for all individuals, irrespective of stool type, for RR of IBS symptoms not improving was 0.98 (95% CI: 0.58 to 1.66). The placebo capsules administered by mouth were higher to capsules comprising donor stool in two of the pooled trials (RR = 1.96; 95% CI: 1.19 to 3.20), and FMT from donor stool distributed through colonoscopy was higher to the autologous stool in two pooled RCTs (RR = 0.63; 95% CI: 0.43 to 0.93); FMT from donor stool through nasojejunal tube exhibited an inclination in the direction of an advantage over an autologous stool in one trial (RR = 0.69; 95% CI: 0.46 to 1.02). The authors concluded that fresh or frozen donor stool distributed by colonoscopy or nasojejunal tube might benefit IBS symptoms. Limitations of the study include a small number of included studies, low quality of reported data, limited generalizability, and heterogeneity. Larger, more thoroughly steered trials of FMT in IBS must conclude the efficacy of FMT for IBS symptoms.

Clinical Practice Guidelines

Agency for Healthcare Research and Quality (AHRQ)

In 2019, the AHRQ created best practices for diagnosing and treating Clostridioides difficile Infections (CDI)s, addressing improving antibiotic use and preventing healthcare-associated infections. Regarding fecal microbiota transplantation (FMT), the AHRQ proposes FMT should be considered for children and adults with multiple CDI recurrences.

American College of Gastroenterology (ACG)

The 2021 ACG guidelines authored by Kelly et al. (2021) suggest FMT be considered for individuals with severe and fulminant CDI refractory to antibiotic therapy, predominantly when they are poor surgical candidates (strong recommendation, low quality of evidence). The ACG recommends FMT to avoid further recurrence in individuals with a second or more CDI recurrence (strong recommendation, moderate quality of evidence). The endorsed delivery method is through colonoscopy or capsules for treating rCDI (strong recommendation, moderate quality of evidence). The ACG suggests enema delivery only if other methods are unavailable (conditional recommendation, low quality of evidence). Repeat FMT is recommended for individuals with a CDI recurrence within eight weeks of the first FMT (conditional recommendation, very low quality of evidence). FMT should be considered for rCDI individuals with IBD (strong recommendation, very low quality of evidence).

American Gastroenterological Association (AGA)

The 2019 AGA guidelines on managing individuals with mild-to-moderate ulcerative colitis (UC) without CDI recommend that FMT be performed only in the context of a clinical trial. Current evidence was rated very low because only small, noncomparative cohort studies of heterogeneous individuals have been completed. AGA noted that extensive studies with long-term follow-up are needed (Ko et al., 2019).

American Society of Colon and Rectal Surgeons (ASCRS)

The 2021 ASCRS guideline for CDI recommends that individuals with recurrent or refractory CDI should typically be considered for fecal bacteriotherapy (e.g., intestinal microbiota transplantation) if conventional measures, including proper antibiotic treatment, have failed (Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B). Poylin et al. (2021), who authored the guidelines, further describe the evidence utilized to develop the guidelines. It is suggested from RCTs, systematic reviews, and meta-analysis that, for individuals with recurrent or refractory CDI where medical management has failed, FMT should be considered, additionally conventional antibiotic treatment should be used for at least two recurrences (i.e., 3 CDI episodes) before offering FMT.

Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

The IDSA-SHEA guidelines contain numerous treatment options for individuals with multiple (i.e., two or more) recurrences of CDI. In addition, FMT is an option for those with multiple recurrences. It is recommended that FMT be reserved for individuals who have established proper antibiotic treatment for at least two episodes of recurrence (or three CDI episodes). This is because of the potential for adverse events such as the transmission of pathogenic organisms, including Escherichia coli and severe acute respiratory syndrome coronavirus 2 (Johnson et al., 2021).

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

In 2021, the ESCMID updated its recommendations on the treatment guidance document for Clostridioides difficile infection in adults (van Prehn et al., 2021). The ESCMID suggests FMT may be a rescue therapy for individuals with severely complex CDI that has declined despite CDI antibiotic treatment and for whom surgery is not an option (Weak, Very Low*).* The ESCMID notes that evidence has shown that FMT has become an acknowledged treatment for multiple recurrent CDI as experience with FMT rises; it has become clear that there might be a role for FMT in severe complicated refractory CDI. The ESCMID recommends treatment opportunities for a second or further CDI recurrence consisting of FMT after SoC antibiotic pre-treatment or bezlotoxumab in addition to standard of care antibiotic treatment; either depends on individual characteristics, earlier treatment, local regulations, obtainability, and practicability. For FMT, a suitable multidisciplinary risk assessment is needed, and FMT products should be obtainable with standardized preparation and screening [Weak, Moderate (FMT) /Low (bezlotoxumab)].

The National Institute for Health and Care Excellence (NICE)

In 2022, NICE published medical technology guidance on FMT for rCDI. NICE recommends FMT as a choice to treat rCDI in adults with two or more previous confirmed episodes based on clinical trial evidence demonstrating FMT treatment's superiority over antibiotics alone at resolving CDI for that population.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

On 11/30/2022, the U.S. Food and Drug Administration approved REBYOTA®, the first fecal microbiota product approved by the agency. REBYOTA® is approved for the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older. It is for use after an individual has completed antibiotic treatment for recurrent CDI. For more information, refer to the following website: https://www.fda.gov/vaccines-blood-biologics/vaccines/rebyota. (Accessed November 27, 2023)

REBYOTA® (fecal microbiota, live-jslm; formerly RBX2660) is a standardized FMT product approved by the FDA for the prevention of rCDI and is not indicated for the treatment of CDI. The treatment is administered rectally as a single dose, prepared from stool donated by qualified individuals. The donors and the donated stool are tested for a panel of transmissible pathogens; however, as REBYOTA® is manufactured from human fecal matter, it may carry a risk of transmitting infectious agents. In addition, the stool may contain food allergens; the potential for the product to cause adverse reactions due to food allergens is unknown. The manufacturer recommends not receiving REBYOTA® if you have a history of a severe allergic reaction (e.g., anaphylaxis) to REBYOTA® or any of its components (REBYOTA., 2022).

References

Agency for Healthcare Research and Quality. Best practices in the diagnosis and treatment of Clostridioides difficile infections [PDF]. (2019, November 1). https://www.ahrq.gov/sites/default/files/wysiwyg/antibiotic-use/best-practices/CDI-facilitator-guide.pdf. Accessed November 27, 2023.

Baunwall SMD, Andreasen SE, Hansen MM, et al. Faecal microbiota transplantation for first or second Clostridioides difficile infection (EarlyFMT): a randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol Hepatol. 2022 Dec;7(12):1083-1091.

Baunwall SMD, Lee MM, Eriksen MK, et al. Faecal microbiota transplantation for recurrent Clostridioides difficile infection: An updated systematic review and meta-analysis. EClinicalMedicine. 2020 Nov 23;29-30:100642.

Brook, I., Albenberg, L., Zong, W., et al. (2022). Anaerobic bacteria. In (Ed.), Principles and practice of pediatric infectious diseases (pp. 1004–1013.e3). Elsevier.

Carlucci C, Petrof EO, Allen-Vercoe E. Fecal microbiota-based therapeutics for recurrent clostridium difficile infection, ulcerative colitis and obesity. EBioMedicine. 2016 Nov;13:37-45.

Cheng F, Huang Z, Wei W, et al. Fecal microbiota transplantation for Crohn's disease: a systematic review and meta-analysis. Tech Coloproctol. 2021 May;25(5):495-504.

Dang X, Xu M, Liu D. Assessing the efficacy and safety of fecal microbiota transplantation and probiotic VSL#3 for active ulcerative colitis: A systematic review and meta-analysis. PLoS One. 2020 Mar 17;15(3):e0228846.

Dubberke ER, Lee CH, Orenstein R, et al. Results from a randomized, placebo-controlled clinical trial of a rbx2660-a microbiota-based drug for the prevention of recurrent clostridium difficile infection. Clin Infect Dis. 2018 Sep 28;67(8):1198-1204.

ECRI. Fecal microbiota Transplantation for Treating Irritable Bowel Syndrome. Plymouth Meeting (PA): ECRI; 2022 Jul. (Clinical Evidence Assessment).

ECRI. Fecal Microbiota Transplantation for Treating Recurrent Clostridioides Difficile Infection. Plymouth Meeting (PA): ECRI; 2018 Sept. Updated 2023 Nov. (Clinical Evidence Assessment).

ECRI. Rebyota (Ferring Pharmaceuticals, Inc.) fecal microbiota transplantation for preventing recurrent Clostridioides difficile infection. Plymouth Meeting (PA): ECRI; 2023 Oct. (Clinical Evidence Assessment).

El Hage Chehade N, Ghoneim S, et al. Efficacy of fecal microbiota transplantation in the treatment of active ulcerative colitis: a systematic review and meta-analysis of double-blind randomized controlled trials. Inflamm Bowel Dis. 2023 May 2;29(5):808-817.

Fehily SR, Basnayake C, Wright EK, et al. Fecal microbiota transplantation therapy in Crohn's disease: Systematic review. J Gastroenterol Hepatol. 2021 Oct;36(10):2672-2686.

Feng J, Chen Y, Liu Y, et al. Efficacy and safety of fecal microbiota transplantation in the treatment of ulcerative colitis: a systematic review and meta-analysis. Sci Rep. 2023 Sep 3;13(1):14494.

Garey KW, Dubberke ER, Guo A, et al. Effect of fecal microbiota, live-jslm (REBYOTA [RBL]) on health-related quality of life in patients with recurrent Clostridioides difficile infection: results from the PUNCH CD3 clinical trial. Open Forum Infect Dis. 2023 Jul 20;10(8):ofad383.

Gutin L, Piceno Y, Fadrosh D, et al. Fecal microbiota transplant for Crohn's disease: a study evaluating safety, efficacy, and microbiome profile. United European Gastroenterol J. 2019 Jul;7(6):807-814. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02460705?term=NCT02460705.&draw=2&rank=1. Accessed November 27, 2023.

Halkjær SI, Lo B, Cold F, et al. Fecal microbiota transplantation for the treatment of irritable bowel syndrome: A systematic review and meta-analysis. World J Gastroenterol. 2023 May 28;29(20):3185-3202.

Hayes, Inc. Health Technology Assessment. Fecal Microbiota Transplantation for the Treatment of Crohn Disease. Hayes, Inc.; May 5, 2022; updated, June 8, 2023.

Hayes, Inc. Health Technology Assessment. Fecal Microbiota Transplantation for the Treatment of Ulcerative Colitis. Hayes, Inc.; August 10, 2021; updated, August 1, 2023.

Holvoet T, Joossens M, Vázquez-Castellanos JF, et al. Fecal microbiota transplantation reduces symptoms in some patients with irritable bowel syndrome with predominant abdominal bloating: short- and long-term results from a placebo-controlled randomized trial. gastroenterology. 2021 Jan;160(1):145-157.e8.

Huang T, Xu J, Wang M, et al. An updated systematic review and meta-analysis of fecal microbiota transplantation for the treatment of ulcerative colitis. Medicine (Baltimore). 2022 Jul 29;101(30):e29790.

Hui W, Li T, Liu W, et al. Fecal microbiota transplantation for treatment of recurrent C. difficile infection: an updated randomized controlled trial meta-analysis. PLoS One. 2019 Jan 23;14(1):e0210016.

Ianiro G, Eusebi LH, Black CJ, et al. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. Aliment Pharmacol Ther. 2019 Aug;50(3):240-248.

Imdad A, Nicholson MR, Tanner-Smith EE, et al. Fecal transplantation for treatment of inflammatory bowel disease. Cochrane Database Syst Rev. 2018 Nov 13;11(11):CD012774.

Iqbal U, Anwar H, Karim MA. Safety and efficacy of encapsulated fecal microbiota transplantation for recurrent Clostridium difficile infection: a systematic review. Eur J Gastroenterol Hepatol. 2018 Jul;30(7):730-734.

Jamshidi P, Farsi Y, Nariman Z et al. Fecal microbiota transplantation in irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. Int J Mol Sci. 2023 Sep 26;24(19):14562.

Jiang ZD, Jenq RR, Ajami NJ, et al. Safety and preliminary efficacy of orally administered lyophilized fecal microbiota product compared with frozen product given by enema for recurrent Clostridium difficile infection: A randomized clinical trial. PLoS

One. 2018 Nov 2;13(11):e0205064. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02449174?term=NCT02449174&draw=2&rank=1. Accessed November 27, 2023.

Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of Clostridioides difficile infection in adults. Clin Infect Dis. 2021 Sep 7;73(5):755-757. Available at: https://www.idsociety.org/practice-guideline/clostridioides-difficile-2021-focused-update/#null. Accessed November 27, 2023.

Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of Clostridioides difficile infections. Am J Gastroenterol. 2021 Jun 1;116(6):1124-1147. Available at: https://journals.lww.com/ajg/Fulltext/2021/06000/ACG_Clinical_Guidelines__Prevention,_Diagnosis,.12.aspx. Accessed November 27, 2023.

Khanna S, Assi M, Lee C, et al. Efficacy and safety of rbx2660 in punch cd3, a phase iii, randomized, double-blind, placebo-controlled trial with a Bayesian primary analysis for the prevention of recurrent Clostridioides difficile infection. Drugs. 2022 Oct;82(15):1527-1538. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03244644?term=rbx2660&draw=2&rank=3. Accessed November 27, 2023.

Ko CW, Singh S, Feuerstein JD, et al. American gastroenterological association institute clinical guidelines committee. aga clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. Gastroenterology. 2019 Feb;156(3):748-764. Available at: https://www.gastrojournal.org/article/S0016-5085(18)35407-6/fulltext. Accessed November 27, 2023.

Lahtinen P, Jalanka J, Mattila E, et al. Fecal microbiota transplantation for the maintenance of remission in patients with ulcerative colitis: A randomized controlled trial. World J Gastroenterol. 2023 May 7;29(17):2666-2678.

Liu X, Li Y, Wu K, et al. Fecal microbiota transplantation as therapy for treatment of active ulcerative colitis: a systematic review and meta-analysis. Gastroenterol Res Pract. 2021 Apr 23;2021:6612970.

Myneedu K, Deoker A, Schmulson MJ. Fecal microbiota transplantation in irritable bowel syndrome: a systematic review and meta-analysis. United European Gastroenterol J. 2019 Oct;7(8):1033-1041.

Narula N, Kassam Z, Yuan Y, et al. Systematic review and meta-analysis: fecal microbiota transplantation for treatment of active ulcerative colitis. Inflamm Bowel Dis. 2017 Oct;23(10):1702-1709.

National Institute for Health and Care Excellence (NICE). MTG71. Faecal microbiota transplant for recurrent Clostridioides difficile infection. August 2022.

Orenstein R, Dubberke E, Hardi R, et al. Safety and durability of rbx2660 (microbiota suspension) for recurrent clostridium difficile infection: results of the punch cd study. Clin Infect Dis. 2016 Mar 1;62(5):596-602. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02299570?term=rbx2660&draw=2&rank=5. Accessed November 27, 2023.

Orenstein R, Dubberke ER, Khanna S, et al. Durable reduction of Clostridioides difficile infection recurrence and microbiome restoration after treatment with rbx2660: results from an open-label phase 2 clinical trial. BMC Infect Dis. 2022 Mar 12;22(1):245. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02589847?term=rbx2660&draw=2&rank=4. Accessed November 27, 2023.

Poylin V, Hawkins AT, Bhama AR, et al. Prepared by the clinical practice guidelines committee of the American Society of Colon and Rectal Surgeons. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the management of Clostridioides difficile infection. Dis colon rectum. 2021 Jun 1;64(6):650-668. https://fascrs.org/healthcare-providers/education/clinical-practice-guidelines. Accessed November 27, 2023.

Ramai D, Zakhia K, Fields PJ, et al. Fecal microbiota transplantation (FMT) with colonoscopy is superior to enema and nasogastric tube while comparable to capsule for the treatment of recurrent Clostridioides difficile infection: a systematic review and meta-analysis. Dig Dis Sci. 2021 Feb;66(2):369-380.

REBYOTA. Prescribing information. Parsippany, NJ: Ferring Pharmaceuticals Inc; 2022.

Rode AA, Chehri M, Krogsgaard LR, et al. Randomised clinical trial: a 12-strain bacterial mixture versus faecal microbiota transplantation versus vancomycin for recurrent Clostridioides difficile infections. Aliment Pharmacol Ther. 2021 May;53(9):999-1009.

Rokkas T, Hold GL. A systematic review, pairwise meta-analysis and network meta-analysis of randomized controlled trials exploring the role of fecal microbiota transplantation in irritable bowel syndrome. Eur J Gastroenterol Hepatol. 2023 Apr 1;35(4):471-479.

Sims MD, Khanna S, Feuerstadt P, et al. Safety and Tolerability of SER-109 as an Investigational Microbiome Therapeutic in Adults With Recurrent Clostridioides difficile Infection: A Phase 3, Open-Label, Single-Arm Trial. JAMA Netw Open. 2023 Feb 1;6(2):e2255758.

Stefansson M, Bladh O, Flink O, et al. Safety and tolerability of frozen, capsulized autologous faecal microbiota transplantation. A randomized double blinded phase I clinical trial. PLoS One. 2023 Sep 27;18(9):e0292132.

Tkach S, Dorofeyev A, Kuzenko I, et al. Fecal microbiota transplantation in patients with post-infectious irritable bowel syndrome: a randomized, clinical trial. Front Med (Lausanne). 2022 Oct 20;9:994911.

van Prehn J, Reigadas E, Vogelzang EH, et al; Guideline committee of the European study group on Clostridioides difficile. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults. Clin Microbiol Infect. 2021 Dec;27 Suppl 2:S1-S21. Available at: https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00568-1/fulltext. Accessed November 27, 2023.

Wang M, Xie X, Zhao S, et al. Fecal microbiota transplantation for irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. Front Immunol. 2023 May 18;14:1136343.

Wu J, Lv L, Wang C. Efficacy of fecal microbiota transplantation in irritable bowel syndrome: a meta-analysis of randomized controlled trials. Front Cell Infect Microbiol. 2022 Feb 28;12:827395.

Xu D, Chen VL, Steiner CA, et al. Efficacy of fecal microbiota transplantation in irritable bowel syndrome: a systematic review and meta-analysis. Am J Gastroenterol. 2019 Jul;114(7):1043-1050.

Zhou S, Cui Y, Zhang Y, et al. Fecal microbiota transplantation for induction of remission in Crohn's disease: a systematic review and meta-analysis. Int J Colorectal Dis. 2023 Mar 8;38(1):62.

Policy History/Revision Information

Date	Summary of Changes
04/01/2024	**Related Policies** • Added reference link to the Medical Benefit Drug Policy titled *Rebyota™ (Fecal Microbiota, Live-Jslm)* **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version CS368.A

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.