Rebyota™ (Fecal microbiota, live-jslm) (for Louisiana Only)

Policy Number: CSLA2023D00124A
Effective Date: TBD

➲ Instructions for Use

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Application

This Medical Benefit Drug Policy only applies to the state of Louisiana.

Coverage Rationale

Rebyota is medically necessary for prevention of the recurrence of CDI in patients who meet all of the following criteria:

- Diagnosis of recurrent clostridioides difficile infection (CDI) as defined by both of the following:
  - Presence of diarrhea defined as a passage of 3 or more loose bowel movements within a 24-hour period for 2 consecutive days;
  - A positive stool test for Clostridioides difficile toxin;

  and
- Patient is 18 years of age or older; **and**
- Patient has had two or more recurrences of CDI following an initial episode of CDI; **and**
- Patient has had antibiotic therapy for at least two episodes of CDI recurrence after the initial CDI episode; **and**
- Both of the following:
  - Patient has completed at least 10 days of one of the following antibiotic therapies for rCDI between 24 to 72 hours prior to initiating Rebyota:
    - Oral vancomycin; **or**
    - Dificid (fidaxomicin)

    and
  - Previous episode of CDI is under control [e.g., less than 3 unformed/loose (i.e., Bristol Stool Scale type 6-7) stools/day for 2 consecutive days]

  and
- Prescribed by or in consultation with one of the following:
  - Gastroenterologist
  - Infectious disease specialist
- Authorization will be issued for a single dose treatment only

Rebyota (fecal microbiota, live-jslm) 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, and irritable bowel syndrome (IBS) due to insufficient evidence of efficacy.

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.

HCPCS Code	Description
J1440	Fecal microbiota, live - jslm, 1 ml
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen

Diagnosis Code	Description
A04.71	Enterocolitis due to Clostridium difficile, recurrent

Background

Clostridium Difficile Infection (CDI): Clostridioides difficile, formerly known as Clostridium difficile, is an anaerobic, grampositive, bacillus bacterium that can be a normal inhabitant of the human colon and is most commonly transmitted via a fecaloral 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.

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).

Rebyota (fecal microbiota, live-jslm) 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 human fecal matter is tested for a panel of transmissible pathogens. Donors do not have dietary restrictions with respect to potential food allergens. The fecal microbiota suspension is the filtrate generated by processing the fecal matter in a predefined ratio with a solution of polyethylene glycol (PEG) 3350 and saline. Each 150mL dose of REBYOTA contains between $1x10^8$ and $5x10^{10}$ colony forming units (CFU) per mL of fecal microbes including >1x105 CFU/mL of *Bacteroides*, and contains not greater than 5.97 grams of PEG3350 in saline. The mechanism of action of Rebyota has not been established.

Clinical Evidence

Proven

Rebyota for Prevention of Recurrent Clostridium Difficile Infection (rCDI)

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 (Rebyota) for the prevention of rCDI. Included in the trial were individuals 18 years or older with one or more Clostridium difficile infection (CDI) recurrences, a positive stool assay for Clostridium difficile 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 (Rebyota). 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.

The results from a randomized, double-blinded, placebo-controlled phase 2B Clinical Trial of RBX2660 (Rebyota) 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, one who received two doses of RBX2660 (group A), a standardized microbiota-based drug, and two who received two doses of placebo (group B), or- three who received one dose of RBX2660 followed by one dose of placebo (group C). 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.

Orenstein et al. aimed to assess the safety and effectiveness of RBX2660 (microbiota suspension) (Rebyota) 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).

Unproven

Fecal Microbiota Transplantation 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 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.

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).

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.

Fecal Microbiota Transplantation 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 2021 (updated in 2022), Hayes conducted a Health Technology Assessment for the use of fecal 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.

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.

Fecal Microbiota Transplantation 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.

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.

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.

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.

Through a systematic review and meta-analysis, Myneedu and colleagues (2020) 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 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 fecal microbiota transplantation (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.

Rebyota (fecal microbiota, live-jslm) is indicated for the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

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Policy History/Revision Information

Date	Summary of Changes
TBD	New policy.

Instructions for Use

This Medical Benefit Drug 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 Benefit Drug 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 Benefit Drug 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.

Archived Policy Versions

Effective Date	Policy Number	Policy Title