Fecal Microbiota Transplantation

Policy # 00441
Original Effective Date: 08/20/2014
Current Effective Date: 03/10/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Fecal microbiota, live-jslm (Rebyota™) is addressed separately in medical policy 00852.

Note: fecal microbiota spores, live-brpk (Vowst™) is addressed separately in medical policy 00858.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider using a conventional compounded fecal microbiota transplantation (FMT) product for treatment of individuals with recurrent *Clostridioides difficile* infection (CDI) to be **eligible for coverage**** (see Policy Guidelines).

Patient Selection Criterion

Coverage eligibility may be considered for a conventional compounded FMT product for treatment of individuals with recurrent CDI when the following criterion is met:

- There have been at least 2 recurrences that are refractory to standard antibiotic treatment.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers fecal microbiota transplantation (FMT) in all other situations to be **investigational.***

The use of fecal microbiota transplantation (FMT) for treatment of individuals with recurrent *Clostridioides difficile* infection (CDI) when patient selection criterion is not met is considered to be **investigational.***

Policy Guidelines

Use of a conventional compounded product refers to a fecal microbiota transplantation (FMT) product not involving a stool bank where the FDA exercises enforcement discretion with respect to

applicable investigational new drug (IND) requirements. For example, this may include FMT products prepared in a hospital laboratory under the direction of licensed health care providers for the purpose of treating their patients provided that the following requirements are met:

1. Physicians obtain adequate informed consent from patients or their legal representative before performing the intervention;
2. Providers perform appropriate screening and testing of the stool donor and stool; and
3. Procedures that mitigate potential safety concerns of FMT are followed.

See the FDA or Other Governmental Regulatory Approval section for additional details.

There is a lack of consensus on the number of recurrences that warrants consideration of fecal microbiota transplantation (FMT).

The 2024 guidelines from the American Gastroenterological Association (AGA) for fecal microbiota-based therapies include 7 recommendations for the use of FMT in gastrointestinal diseases including *Clostridioides difficile* infection (CDI) (Peery et al, 2024; PMID 38395525). The guidelines consider FMT to be an option for immunocompetent individuals after the second recurrence (third episode). The AGA considers the degree of immunocompromise as a qualifier the use of CD in select individuals at high risk of either recurrent CDI or a morbid CDI recurrence.(See Supplemental Information) The AGA defined recurrent CDI as "clinically significant diarrhea with a confirmatory positive test within 8 weeks of completing antibiotics for CDI."

The 2021 focused update of the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guideline for *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI) states that individuals with multiple recurrences of CDI who have failed to resolve their infection with standard of care antibiotic treatments are potential candidates for FMT (Johnson et. al., 2021; PMID 34164674). It was the opinion of guideline panelists to have individuals try appropriate antibiotics for at least 2 recurrences (ie, 3 CDI episodes) before FMT is considered. The optimal timing between multiple FMT sessions is not discussed in the guidelines.

The 2021 American Society of Colon and Rectal Surgeons (ASCRS) guideline for CDI recommends that individuals with 3 or more CDI episodes be managed with a vancomycin tapered and pulsed course or fidaxomicin followed by a microbiome-based therapy such as FMT (Povlin et. al., 2021; PMID 33769319). Per the guideline: “Conventional antibiotic treatment should be used for at least 2 recurrences (ie, 3 CDI episodes) before offering fecal microbiota transplantation." Per Table 3 in this guideline: for "Third or Subsequent” CDI episode: "If FMT is available, then 10-day course of vancomycin followed by FMT.”

The 2021 American College of Gastroenterology (ACG) guideline for CDI recommends FMT for individuals experiencing their second or further recurrence of CDI (ie, third or later CDI episode) to prevent further recurrences (Kelly et. al, 2021; PMID 34003176). This guideline also specifically

recommends a repeat FMT for individuals experiencing a recurrence of CDI within 8 weeks of an initial FMT session.

Per the 2017 IDSA/SHEA guideline, a recurrent case occurs within 2 to 8 weeks of the incident case and requires both clinical plus laboratory evidence of disease for diagnosis; the 2021 IDSA/SHEA guideline does not provide an update to this definition. The 2021 guidelines from the ASCRS and ACG define a recurrent case as one occurring within 8 weeks after the completion of a course of CDI therapy and requiring both clinical plus laboratory evidence of disease for diagnosis (Povlin et. al., 2017; PMID 33769319).

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

- Donor screening with questions that specifically address risk factors for colonization with multi-drug resistant organisms (MDROs), and exclusion of individuals at higher risk of colonization with MDROs.
- MDRO testing of donor stool and exclusion of stool that tests positive for MDRO. FDA scientists have determined the specific MDRO testing and frequency that should be implemented.
- Consent for the use of FMT is obtained from the individual or a legally authorized representative in accordance with FDA guidance (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-regarding-investigational-new-drug-requirements-use-fecal-microbiota-0).

On April 9, 2020, the FDA published additional safety information regarding the potential risk of transmission of SARS-CoV-2 via FMT. Recommendations for additional screening and testing procedures are outlined in this publication (https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-new-safety-information-regarding-additional-protections-screening).

On August 20, 2022, the FDA also published a safety alert regarding the use of FMT and additional safety protections pertaining to the monkeypox virus (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections-0).

Background/Overview

Fecal Microbiota

Fecal microbiota transplantation (FMT), also called donor feces infusion, intestinal microbiota transplantation, and fecal bacteriotherapy involves the duodenal infusion of intestinal microorganisms via the transfer of stool from a healthy individual into a diseased individual to restore normal intestinal flora. The stool can be infused as a liquid suspension into a patient's upper

gastrointestinal tract through a nasogastric tube or gastroscopy, into the colon through a colonoscope or rectal catheter, or administered orally via capsules (ie, encapsulated FMT). Traditionally, the material used for FMT was prepared either within hospital facilities or at stool banks. More recently, FDA-approved FMT therapies have also come onto the market (see FDA or Other Governmental Regulatory Approval section below).

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

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

Applications

Clostridioides difficile Infection

To date, the major potential clinical application of FMT is in the treatment of *Clostridioides difficile* infection (CDI). Infection of the colon with *C. difficile* is a major cause of colitis and can cause life-threatening conditions including colonic perforation and toxic megacolon. *C.difficile* occurs naturally in the intestinal flora. According to the 2019 Centers for Disease Control and Prevention (CDC) report, *Antibiotic Resistance Threats in the United States*, CDI continues to be an urgent threat. In 2017, there were an estimated 223,900 cases of CDI in hospitalized patients and an estimated 12,900 CDI-associated deaths. Interestingly, the overall number of cases of healthcare-associated CDI cases has been trending down since 2012 when the number of cases was estimated at 251,400.

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

Other Applications

Other potential uses of FMT include the treatment of conditions in which altered colonic flora may play a role: inflammatory bowel disease, irritable bowel syndrome, idiopathic constipation, and non-

gastrointestinal diseases such as multiple sclerosis, obesity, autism, and chronic fatigue syndrome. However, for these conditions, the contribution of alterations in colonic flora to the disorder is uncertain or controversial.

There is interest in alternatives to human feces that might have the same beneficial effects on intestinal microbiota without the risks of disease transmission. In a proof of principle study, Petrof et al (2013) evaluated a synthetic stool product in 2 patients with recurrent CDI. The product is made from 33 bacterial isolates developed from culturing stool from a healthy donor.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 2022, the U.S. Food and Drug Administration (FDA) finalized guidance on investigational new drug (IND) requirements for the use of FMT to treat CDI not responsive to medication therapy. The guidance states that the previous policy of enforcement discretion does not apply to fecal microbiota that is obtained from a stool bank due to safety concerns related to the number of patients that may be exposed to a particular donor and centralized manufacturing practices. As a result, sponsors must comply with IND requirement in these settings. The guidance defines a stool bank as "an establishment that collects, prepares, and stores FMT product for distribution to other establishments, health care providers, or other entities for use in patient therapy or clinical research. An establishment that collects or prepares FMT products solely under the direction of licensed health care providers for the purpose of treating their patients (e.g., a hospital laboratory) is not considered to be a stool bank under this guidance."

The agency will continue to use enforcement discretion regarding the use of fecal transplant to treat treatment-resistant CDI when FMT product is not obtained from a stool bank and where:

1. physicians obtain adequate informed consent from patients or their legal representative before performing the intervention;
2. providers perform appropriate screening and testing of the stool donor and stool; and
3. procedures that mitigate potential safety concerns of FMT are followed. The document also noted that selective enforcement does not apply to the use of fecal transplant for treating conditions other than treatment-resistant CDI.

In 2019, the FDA issued a safety alert regarding the use of FMT due to the potential risk of serious or life-threatening infections caused by the transmission of multi-drug resistant organisms (MDROs). Two immunocompromised individuals received investigational FMT and developed invasive infections caused by the transmission of extended-spectrum beta-lactamase-producing *Escherichia coli*. One of the affected individuals died. The donor stool used in each patient's FMT procedures had not been tested for extended-spectrum beta-lactamase-producing gram-negative organisms prior to use. Follow-up testing verified donor stool was positive for MDROs identical to

the organisms isolated from the 2 patients. Due to these events, the FDA has determined that the following additional protections are required for any investigational use of FMT:

- Donor screening that specifically addresses risk factors for colonization with MDROs and exclusion of individuals at higher risk of colonization with MDROs (eg, health care workers, persons who have recently been hospitalized or discharged from long-term care facilities, persons who regularly attend outpatient medical or surgical clinics, and persons who have recently engaged in medical tourism).
- MDRO testing of donor stool and exclusion of stool testing positive for MDROs. At a minimum, tests should include:
    - extended-spectrum beta-lactamase-producing *Enterobacteriaceae*
    - vancomycin-resistant enterococci
    - carbapenem-resistant *Enterobacteriaceae*
    - methicillin-resistant *Staphylococcus aureus*
- All FMT products currently in storage for future use must be quarantined until donor MDRO carriage risk can be assessed and FMT products are tested and found negative for MDROs.
- The informed consent process for FMT treatment subjects should describe the risk of MDRO transmission and infection and the measures being implemented for donor screening and stool testing.

In 2022, the FDA approved the first fecal microbiota product, Rebyota™‡ (fecal microbiota, live-jslm). Rebyota is approved for the prevention of recurrence of CDI in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI. Importantly, the drug is not approved for the treatment of CDI. Rebyota is supplied as a 150 mL suspension for rectal administration as a single dose, 24 to 72 hours after the last dose of antibiotics for CDI.

In 2023, the FDA approved the first orally administered fecal microbiota product, Vowst™‡(fecal microbiota spores, live–brpk). Similar to Rebyota, Vowst is approved for the prevention of recurrence of CDI in individuals 18 years of age and older following antibiotic treatment for recurrent CDI, and is not approved for the treatment of CDI. The drug is administered as 4 capsules by mouth once daily for 3 consecutive days.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Fecal Microbiota Transplantation

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Description
Fecal microbiota transplantation (FMT) involves the administration of intestinal microorganisms via the transfer of stool from a healthy person into a diseased individual , with the intent of restoring normal intestinal flora. Fecal transplant is proposed for treatment-refractory *Clostridioides* (formerly *Clostridium) difficile* infection (CDI) and other conditions, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), pouchitis, constipation, multi-drug resistant organism (MDRO) infection, or metabolic syndrome.

Summary of Evidence
For individuals who have recurrent *Clostridioides difficile* infection (CDI) refractory to antibiotic therapy who receive fecal microbiota transplantation (FMT) with a conventional compounded product, the evidence includes systematic reviews with meta-analyses and observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Meta-analyses have found that FMT is more effective than standard treatment or placebo for patients with recurrent CDI. A long-term prospective study found that FMT for recurrent or refractory CDI appears to be durable at 4 to 8 years following treatment, even for patients who had subsequently received non-CDI antibiotic therapy. A meta-analysis comparing several routes of FMT delivery for the treatment of recurrent CDI found that cure rates were significantly higher with colonoscopy or oral capsules versus nasogastric tube or enema, while colonoscopy and capsules were equally effective. Similar success rates have been demonstrated with FMT using fresh versus frozen feces. Conversely, data regarding the superiority of FMT using donor versus autologous feces are conflicting. Few treatment-related adverse events have been reported. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have inflammatory bowel disease (IBD) who receive FMT, the evidence includes systematic reviews and RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Systematic reviews have generally shown favorable clinical remission and response with FMT in patients with IBD while acknowledging that further RCTs and long-term follow-ups are needed to assess long-term effectiveness and safety. Additionally, a Cochrane review found that FMT did not significantly improve the maintenance of clinical or endoscopic remission of ulcerative colitis (UC). A 48-week RCT in patients with UC in clinical remission after prior FMTs found conflicting results for remission outcomes with additional courses of FMT. Another RCT in patients with recurrent active UC found a median remission time of 24 months in both FMT and standard of care treatment groups. A 12-month RCT evaluating FMT for the maintenance of remission in patients with UC did not find a statistically significant difference between single-dose FMT and control groups. This current evidence is not sufficient to permit conclusions on the efficacy of FMT for UC. Additionally, questions remain about the optimal route of administration, donor characteristics, and the number of transplants. An RCT in patients with Crohn disease (CD) failed to find a difference in the achievement of remission with FMT versus placebo. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have irritable bowel syndrome (IBS) who receive fecal microbiota transplantation (FMT) the evidence includes systematic reviews and RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. For individuals who have IBS who receive FMT, the evidence includes systematic reviews and RCTs. Systematic reviews with meta-analyses have been inconsistent in finding improvements in clinical response, IBS Severity Scoring System, or IBS Quality of Life scores with FMT compared to placebo. Two additional RCTs also utilized autologous FMT as a placebo, and did not find a significant reduction in symptoms of IBS using donor FMT; both trials also found reduced durability of response 1 year following donor FMT. An additional placebo-controlled RCT used FMT delivered via oral capsules and found no improvement in abdominal pain scores, stool frequency, or stool form in a mixed population of patients with IBS. Few treatment-related adverse events have been reported. Data are limited by heterogeneity in utilized outcome measurement scales and definitions of treatment response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 5 clinicians associated with 3 physician specialty societies and from 5 clinicians at 2 academic medical centers while this policy was under review in 2014. There was near consensus that fecal transplantation may be considered medically necessary for treating at least some patients with *Clostridioides difficile* infection (CDI). There was also near

consensus that fecal microbiota transplant (FMT) is considered investigational for inflammatory bowel disease; moreover, there was a consensus that FMT is considered investigational for conditions other than those previously mentioned. Input was mixed on criteria for selecting patients with CDI for fecal transplantation; in general, the number of FMT recurrences was considered an important criterion. There was a near consensus among reviewers that there are potential safety concerns associated with FMT, and that these concerns should be studied further before the procedure is offered routinely in clinical practice.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology
In 2019, the American College of Gastroenterology (ACG) published guidelines on the management of adults with ulcerative colitis (UC). The guidelines noted "fecal microbiota transplantation (FMT) requires more study and clarification of treatment before use as therapy for UC."

In 2021, the ACG published a guideline on the management of *Clostridioides difficile* infection (CDI). This guideline makes the following recommendations:

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

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

American Gastroenterological Association

In 2024, the American Gastroenterological Association (AGA) released guidelines for fecal microbiota-based therapies including recommendations for the use of FMT in several gastrointestinal (GI) diseases including CDI, UC, Crohn disease (CD), pouchitis, and IBS. The AGA recommends the following:

- "In immunocompetent adults with recurrent *C difficile* infection, the AGA suggests the use of fecal microbiota–based therapies upon completion of standard of care antibiotics over no fecal microbiota–based therapies. (Conditional recommendation, low certainty evidence)". The recommendations further specify that conventional (compounded, donor), fecal microbiota live-jslm, and fecal microbiota spores live-brpk are all included in this recommendation.
- "In mildly or moderately immunocompromised adults with recurrent *C difficile* infection, the AGA suggests the use of conventional fecal microbiota transplant upon completion of standard of care antibiotics over no fecal microbiota transplant. (Conditional recommendation, very low certainty of evidence) In severely immunocompromised adults with recurrent *C difficile* infection, the AGA suggests against the use of fecal microbiota based therapies upon completion of standard of care antibiotics over no fecal microbiota–based therapies. (Conditional recommendation, very low certainty of evidence)". Severely immunocompromised individuals include "patients receiving active cytotoxic therapy for solid tumors and hematologic malignancies, patients who have received chimeric antigen receptor T-cell therapy or hematopoietic cell transplant (only when neutropenic), any neutropenia, patients with severe primary immunodeficiency, patients with advanced or untreated HIV infection (CD4 counts <200/mm3, AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)." All other immunocompromised patients are considered to be mild or moderate when they do not meet the definition of severe immunocompromise.
- "In adults hospitalized with severe or fulminant *C difficile* infection not responding to antimicrobial therapy, the AGA suggests the use of conventional fecal microbiota transplant over no fecal microbiota transplant. (Conditional recommendation, very low certainty of evidence)". Severe CDI includes individuals with a leukocyte count of 15 x 10^9 cells/L or more and/or creatinine of 1.5 mg/dL or more. Fulminant CDI is severe CDI with shock, ileus, or megacolon. The AGA also states, "FMT should be performed with appropriately screened donor stool. There is no evidence for using the FDA-approved fecal microbiota based therapies as adjuvant treatment in severe or fulminant CDI."

The AGA "suggests against the use of conventional fecal microbiota transplant, except in the context of clinical trials" for adults with UC, CD, pouchitis, or IBS.

American Society of Colon and Rectal Surgeons
In 2021, the American Society of Colon and Rectal Surgeons (ASCRS) published a guideline on the management of CDI. This guideline states that:

- "Patients with recurrent or refractory CDI should typically be considered for fecal bacteriotherapy (eg, intestinal microbiota transplantation) if conventional measures, including appropriate antibiotic treatment, have failed (Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B)."
- "Patients with 3 or more CDI episodes can be managed with a vancomycin tapered and pulsed course or fidaxomicin followed by a microbiome-based therapy such as fecal microbiota transplantation."
- "In general, conventional antibiotic treatment should be used for at least 2 recurrences (ie, 3 CDI episodes) before offering fecal microbiota transplantation."

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

Infectious Diseases Society of America and Society for Healthcare Epidemiology of America
In 2017, the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America updated clinical practice guidelines for the diagnosis and treatment of CDI in children and adults. Recommendations were summarized as follows:

- "Consider fecal microbiota transplantation for pediatric patients with multiple recurrences of CDI following standard antibiotic treatments. (Weak recommendation, very low quality of evidence)"
- "Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments. (Strong recommendation, moderate quality of evidence)"
- "Potential candidates for FMT include patients with multiple recurrences of CDI who have failed to resolve their infection despite treatment attempts with antibiotic agents targeting CDI. Although there are no data to indicate how many antibiotic treatments should be attempted before referral for FMT, the opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried."

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

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

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05831189	A Multi-center, Single-arm Trial Exploring the Safety and Clinical Effectiveness of RBX2660 Administered by Colonoscopy to Adults With Recurrent Clostridioides Difficile Infection (CDI-SCOPE)	41*	Jan 2025
NCT04997733	Fecal Microbiota Transplantation in Crohn's Disease as Relay After Anti-TNF Withdrawal (MIRACLE)	150	Jul 2027 (recruiting)
NCT04691544	Donor Versus Autologous Fecal Microbiota Transplantation for Irritable Bowel Syndrome: a Double Blind, Placebo-Controlled, Randomized Trial	450	Dec 2026
NCT05035342	Fecal Transplantation to Eradicate Colonizing Emergent Superbugs (FECES)	214	Apr 2028 (recruiting)
NCT04746222	Oral Capsule-administered Faecal Microbiota Transplantation for Intestinal Carbapenemase-producing Enterobacteriaceae Decolonization	108	Jul 2023 (unknown)
NCT04970446	The MIRO II Study: Microbial Restoration in Inflammatory Bowel Diseases	120	Dec 2025 (recruiting)
NCT02269150	A Randomized Controlled Trial of Autologous Fecal Microbiota Transplantation (Auto-FMT)	59*	Oct 2025 (ongoing)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	for Prophylaxis of Clostridium Difficile Infection in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation		
NCT03562741	Outcomes and Data Collection for Fecal Microbiota Transplantation for the Treatment of Recurrent Clostridium Difficile	500	Jan 2027 (recruiting)
NCT03804931	Efficacy and Safety of Fecal Microbiota Transplantation for Ulcerative Colitis	120	Dec 2030 (recruiting)
NCT03613545	Efficacy and Safety of Fecal Microbiota Transplantation for Irritable Bowel Syndrome	120	Dec 2030 (recruiting)
NCT04521205	A Multicenter Clinical Trial: Efficacy, Safety of Fecal Microbiota Transplantation for Inflammatory Bowel Disease	200	Apr 2024 (recruiting)
NCT06001333	Efficacy and Safety of Fecal Microbiota Transplantation for the Decolonization of Multidrug-Resistant Organisms in the Intestinal Tract: An Unblinded Randomized Controlled Trial	240	Dec 2026 (recruiting)
NCT06433180	A Prospective, Multi-center, Double Blind Randomized Trial of Fecal Microbiota Transplantation (FMT) Delivered by Capsule Versus Placebo in Severe Irritable Bowel Syndrome (IBS)	150	Jul 2029 (not yet recruiting)
Unpublished			
NCT02255305	Fecal Microbiota Transplantation Versus Standard Medical Therapy for Initial Treatment of Recurrent Clostridium Difficile Infection	6	Jan 2020 (terminated)
NCT03834038	Prospective, Open-label Trial to Evaluate Efficacy of Lyophilized Fecal Microbiota Transplantation for Treatment of Recurrent C. Difficile Infection	158*	Mar 2020 (completed)
NCT04100291	The Effect of Faecal Microbiota Transplantation in the Treatment of Chronic Pouchitis: A	30*	Mar 2022 (terminated)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Multicentre, Placebo-controlled, Randomized, Double Blinded Trial		

NCT: national clinical trial.
* Reflects actual enrollment.

References

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4. Food and Drug Administration (FDA). Guidance for Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies. 2022; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-regarding-investigational-new-drug-requirements-use-fecal-microbiota.
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Policy History

Original Effective Date: 08/20/2014
Current Effective Date: 03/10/2025

08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. New policy.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. No change in coverage.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. No change in coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/09/2018	Medical Policy Committee review

Fecal Microbiota Transplantation

Policy # 00441
Original Effective Date: 08/20/2014
Current Effective Date: 03/10/2025

08/15/2018	Medical Policy Implementation Committee approval. Changed the number of recurrent infection episodes from "2 "to "3" in the first bullet of the Patient Selection Criteria. Added a Policy Guidelines section.
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Eligible for coverage statement updated with information from 2017 IDSA guidelines for C. diff regarding the number of prior CDIs before FMT is considered with Patient Selection Criterion: • There have been at least 2 recurrences that are refractory to standard antibiotic treatment"). Policy Guidelines section updated with FDA warning regarding donor screening and testing of donor stool. Policy Guidelines section updated with FDA warning regarding donor screening and testing of donor stool.
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2022	Coding update
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Changed "patients" to "individuals" throughout the policy. Coverage eligibility unchanged.
02/01/2024	Medical Policy Committee review
02/14/2024	Medical Policy Implementation Committee approval. Added description of fecal microbiota transplantation as a compounded product in the eligible for coverage section. Coverage eligibility unchanged.
02/06/2025	Medical Policy Committee review
02/12/2025	Medical Policy Implementation Committee approval. Added "conventional" to compounded fecal microbiota transplantation and removed a reference to the U.S Food and Drug Administration Guidance in the Eligible for Coverage and Patient Selection Criterion statements. Policy Guidelines updated with 2024 American Gastroenterological Association (AGA) Guidelines. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2026

Fecal Microbiota Transplantation

Policy # 00441
Original Effective Date: 08/20/2014
Current Effective Date: 03/10/2025

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0780T, 44705
HCPCS	G0455
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.