



Louisiana

Fecal Microbiota Transplantation

Policy # 00441

Original Effective Date: 08/20/2014

Current Effective Date: 03/08/2021

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.

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 fecal microbiota transplantation (FMT) for treatment of patients with recurrent *Clostridium difficile* infection (CDI) to be **eligible for coverage**** (see Policy Guidelines section for U.S. Food and Drug Administration Guidance).

Patient Selection Criterion

Coverage eligibility may be considered for FMT for treatment of patients with recurrent CDI when all of 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 patients with recurrent CDI when patient selection criteria are not met is considered to be **investigational.***

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Policy Guidelines

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

The 2017 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines for *Clostridioides difficile* infection state that patients with multiple recurrences of CDI who have failed to resolve their infection with standard of care antibiotic treatments are potential candidates for FMT. It was the opinion of guideline panelists to have patients 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. Per the 2017 IDSA and Society for Healthcare Epidemiology of America (SHEA) guidelines for *Clostridioides difficile* infection, a recurrent case occurs within 2 to 8 weeks of the incident case and requires both clinical plus laboratory evidence of disease for diagnosis.

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 patient or a legally authorized representative in accordance with FDA guidance.

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.

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

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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, or the stool can be infused into the colon through a colonoscope or rectal catheter.

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

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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 2016, the U.S. Food and Drug Administration (FDA) issued updated draft guidance on investigational new drug requirements for the use of FMT to treat CDI not responsive to medication therapy. The draft guidance is similar to the 2013 guidance and states that the FDA is continuing to consider how to regulate FMT and that, during this interim period, the agency will use enforcement discretion regarding the use of fecal transplant to treat treatment-resistant CDI. The FDA requires that physicians obtain adequate informed consent from patients or their legal representative before performing the intervention. The document also noted that selective enforcement does not apply to the use of fecal transplant for treating conditions other than treatment-resistant CDI.

In 2019, the FDA issued a safety alert regarding the use of FMT due to the potential risk of serious or life-threatening infections caused by the transmission of multi-drug resistant organisms (MDROs). 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

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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.

Rationale/Source

Fecal microbiota transplantation (FMT) involves the administration of intestinal microorganisms via the transfer of stool from a healthy person into a diseased patient, 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.

For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT, 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

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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 a meaningful improvement in the net health outcome.

For individuals who have irritable bowel disease who receive FMT, the evidence includes systematic reviews and RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Two systematic reviews with meta-analysis concluded that FMT had shown promise in treating patients with ulcerative colitis, but 1 meta-analysis recommended caution about using FMT to treat patients with Crohn disease. A 48-week RCT in patients with ulcerative colitis in clinical remission after prior FMTs found conflicting results for remission outcomes with additional courses of FMT. This current evidence is not sufficient to permit conclusions on the efficacy of FMT for ulcerative colitis. Additionally, questions remain about the optimal route of administration, donor characteristics, and the number of transplants. A small RCT in patients with Crohn disease failed to find a difference in the achievement of remission with FMT versus placebo. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have irritable bowel syndrome who receive FMT, the evidence includes a systematic review and RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The systematic review with meta-analysis reviewed 5 RCTs and reported mixed outcomes for FMT in patients with irritable bowel syndrome. When all studies were pooled, no net benefit was found for active FMT. In a pooled analysis of 3 RCTs utilizing autologous FMT as a placebo, patients were less likely to experience an improvement in IBS symptoms with donor FMT (ie, active treatment). Two additional RCTs published after the meta-analysis also utilized autologous FMT as a placebo, and did not find a significant reduction in symptoms of irritable bowel syndrome using donor FMT; both trials also found reduced durability of response 1 year following donor FMT. Few treatment-related adverse events have been reported. Data are limited by small study sizes and heterogeneity in utilized outcome measurement scales and definitions of treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

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For individuals who have pouchitis, constipation, multidrug-resistant organism infection, or metabolic syndrome who receive FMT, the evidence includes systematic reviews and an RCT. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Systematic reviews of data from patients who received FMT for constipation, pouchitis, multidrug-resistant organisms, 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. An RCT comparing FMT to no intervention in patients with multidrug-resistant organisms failed to demonstrate improved rates of decolonization with treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

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Practice Guidelines and Position Statements

American College of Gastroenterology

In 2019, the American College of Gastroenterology published guidelines on the management of adults with ulcerative colitis. The guidelines addressed FMT as therapy for induction of remission, as follows:

"Fecal microbiota transplantation (FMT) requires more study and clarification of treatment before use as therapy for UC."

Infection 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."

British Society of Gastroenterology

In 2019, the British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults made the following recommendation regarding FMT:

- "We suggest that faecal microbiota transplantation (FMT) shows some evidence of benefit in ulcerative colitis and should be used in the context of clinical trials until further high-quality evidence clarifies the potential for benefit and optimal administration protocol (GRADE: weak recommendation, moderate-quality evidence. Agreement: 93.3%)."

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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
<i>Ongoing</i>			
NCT03167398	Fecal Microbiota Transplantation for Eradication of Carbapenem-resistant Enterobacteriaceae Colonization	60	Dec 2019 (completed)
NCT02255305	Fecal Microbiota Transplantation Versus Standard Medical Therapy for Initial Treatment of Recurrent Clostridium Difficile Infection	60	Dec 2019 (recruiting)
NCT02592343	Prospective, Open-label Trial to Evaluate Efficacy of Lyophilized Fecal Microbiota Transplantation for Treatment of Recurrent C. Difficile Infection	100	Sept 2020 (completed)
NCT02269150	A Randomized Controlled Trial of Autologous Fecal Microbiota Transplantation (Auto-FMT) for Prophylaxis of Clostridium Difficile Infection in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation	59*	Oct 2021 (ongoing)

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03562741	Outcomes and Data Collection for Fecal Microbiota Transplantation for the Treatment of Recurrent Clostridium Difficile	500	Jan 2023 (recruiting)
NCT03804931	Efficacy and Safety of Fecal Microbiota Transplantation for Ulcerative Colitis	120	Dec 2030 (recruiting)
NCT04521205	A Multicenter Clinical Trial: Efficacy, Safety of Fecal Microbiota Transplantation for Inflammatory Bowel Disease	200	Apr 2024 (recruiting)
NCT04100291	The Effect of Faecal Microbiota Transplantation in the Treatment of Chronic Pouchitis: A Multicentre, Placebo-controlled, Randomized, Double Blinded Trial	50	Jun 2021 (recruiting)

NCT: national clinical trial.

* Reflects actual enrollment.

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- Exposure to SARS-CoV-2 and Testing for SARS-CoV-2. 2020; <https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-new-safety-information-regarding-additional-protections-screening>.
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- | | |
|------------|---|
| 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 |

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- 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.

Next Scheduled Review Date: 02/2022

Coding

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

Code Type	Code
CPT	44705
HCPCS	G0455
ICD-10 Diagnosis	A04.7

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

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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.

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