



Louisiana

Fecal Microbiota Transplantation

Policy # 00441

Original Effective Date: 08/20/2014

Current Effective Date: 09/14/2020

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).

Patient Selection Criteria

Coverage eligibility may be considered for FMT for treatment of patients with recurrent CDI when all of the following criteria are met:

- There have been at least 3 episodes of recurrent infection; and
- Episodes are refractory to appropriate antibiotic regimens, including at least 1 regimen of pulsed vancomycin.

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).

Among the published randomized controlled trials evaluating FMT for treatment of *Clostridium difficile* infection (CDI), the van Nood study (2013) included patients with at least 1 recurrence of CDI; the other study, the Youngster study (2014), included patients with a relapse after at least 3 episodes of mild-to-moderate CDI or at least 2 episodes of severe CDI (both studies are described in the Rationale section.)

The 2013 American College of Gastroenterology guidelines have recommended that FMT be considered second-line therapy for a third recurrence of CDI.

Background/Overview

Fecal Microbiota

Fecal microbiota transplantation (FMT), also called donor feces infusion, intestinal microbiota transplantation, and fecal bacteriotherapy involves the 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, 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 (ie, 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,

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repressing the growth of pathogenic microbes, and stimulating the lymphoid tissue to produce antibodies to pathogens.

Applications

***Clostridium difficile* Infection**

To date, the major potential clinical application of FMT is the treatment of *Clostridium 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. The incidence of CDI in North America has increased substantially. For example, according to hospital discharge diagnosis data, there were more than 300000 cases of CDI in 2006 compared with fewer than 150000 cases in 2000. Moreover, CDI causes an estimated 15000 to 20000 deaths per year in U.S. hospitals.

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 treatment of conditions in which altered colonic flora may play a role. They include 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.

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

- Donor screening that specifically addresses risk factors for colonization with MDROs and exclusion of individuals at higher risk of colonization with MDROs (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.

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Louisiana

Fecal Microbiota Transplantation

Policy # 00441

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Current Effective Date: 09/14/2020

- 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 infusion 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 *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 randomized controlled trials (RCTs), multiple systematic reviews, and observational studies. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The RCTs found that FMT was more effective than standard treatment or placebo for patients with recurrent CDI. Other RCTs did not find the superiority of any route of administration over another or the superiority of fresh vs frozen feces. Case reports and case series have reported high rates of resolution of recurrent CDI following treatment with FMT. 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 inflammatory bowel disease who receive FMT, the evidence includes a large-scale systematic review and meta-analysis, two RCTs in patients with ulcerative colitis, as well as observational studies. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Two small RCTs on FMT for treatment of ulcerative colitis were discontinued due to futility, which restricted data analysis to patients already enrolled. Of the 2 small RCTs, one found a statistically significant higher remission rate after active FMT than after a control intervention, but this trial had few patients in remission (n=11) and short follow-up (7 weeks); the other trial reported no difference in remission rates. Data on a small number of patients with Crohn disease are available; however, there are no controlled studies of FMT in this population. 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. The relevant outcomes are symptoms, change in disease status, and

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treatment-related morbidity. The systematic review found mixed outcomes; in a pooled analysis of three RCTs utilizing autologous FMT as a placebo, the relative risk of irritable bowel syndrome symptoms not improving decreased and was statistically superior compared to 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.

For individuals who have pouchitis, constipation, multi-drug resistant organism infection, or metabolic syndrome who receive FMT, the evidence includes a small number of case series and RCTs. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Data are available for only a limited number of patients and there is a lack of comparative studies. Current comparative studies are small and either do not report clinical outcomes or fail to demonstrate a significant benefit. 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 *Clostridium 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

The American College of Gastroenterology (2013) published guidelines on diagnosis, treatment, and prevention of CDI. The guidelines addressed fecal microbiota transplant for treatment of three or more CDI recurrences, as follows:

"If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)"

For the treatment of one to two CDI recurrences, the guidelines recommend:

"The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. If severe, however, vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen. (Conditional recommendation, low-quality evidence)"

The American College of Gastroenterology (2019) published guidelines on the management of adults with ulcerative colitis. The guidelines addressed fecal microbiota transplant 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

The Infectious Diseases Society of America and Society for Healthcare Epidemiology of America updated clinical practice guidelines (2019) for the diagnosis and treatment of CDI in children and adults. 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)"

U.S. Preventive Services Task Force Recommendations

Not applicable.

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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>			
NCT02526849	A Randomized Controlled Study of Efficacy, Safety and Durability of Fecal Microbiota Transplantation in Adult Patients With Slow Transit Constipation	100	Jun 2017 (unknown)
NCT03167398	Fecal Microbiota Transplantation for Eradication of Carbapenem-resistant Enterobacteriaceae Colonization	60	Oct 2019 (recruiting)
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	Jan 2020 (ongoing)
NCT03015467	Alteration of Intestinal Microflora and Efficacy and Safety of Fecal Microbiota Transplantation for Severe Acute Pancreatitis	80	Mar 2020 (recruiting)
NCT02269150	A Randomized Controlled Trial of Autologous Fecal Microbiota Transplantation (Auto-FMT) for	59*	Oct 2020 (ongoing)

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NCT No.	Trial Name	Planned Enrollment	Completion Date
	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 2023 (recruiting)
NCT03804931	Efficacy and Safety of Fecal Microbiota Transplantation for Ulcerative Colitis	120	Dec 2030 (recruiting)

NCT: national clinical trial.

* Reflects actual enrollment.

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Louisiana

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Policy # 00441

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Current Effective Date: 09/14/2020

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Louisiana

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Current Effective Date: 09/14/2020

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Policy History

Original Effective Date: 08/20/2014

Current Effective Date: 09/14/2020

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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.

Next Scheduled Review Date: 08/2021

Coding

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Louisiana

Fecal Microbiota Transplantation

Policy # 00441

Original Effective Date: 08/20/2014

Current Effective Date: 09/14/2020

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);
 - 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

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- 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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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