MASSACHUSETTS

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Medical Policy

Fecal Microbiota Transplantation

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Policy Number: 682

BCBSA Reference Number: 2.01.92 (For Plan internal use only)
NCD/LCD: N/A

Related Policies

Fecal Analysis in the Diagnosis of Intestinal Dysbiosis, #556

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Fecal microbiota transplantation using a non-commercially prepared product may be considered **MEDICALLY NECESSARY** for treatment of individuals with recurrent *Clostridium difficile* infection under the following condition:

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

Fecal microbiota transplantation using a commercially prepared FDA approved product* may be considered **MEDICALLY NECESSARY** for the treatment of individuals with recurrent Clostridioides difficile infection under the following condition:

- There have been at least 2 recurrences that are refractory to standard antibiotic treatment; and
- The recipient is 18 years of age or older.

Fecal microbiota transplantation is considered **INVESTIGATIONAL** in all other situations.

*In 2022, the FDA approved the first fecal microbiota product, Rebyota™ (fecal microbiota, live-jslm).[6] 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).[7] 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.

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

The 2021 focused update of the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guideline for *Clostridioides 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).

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.
Medicare HMO Blue℠	Prior authorization is **not required**.
Medicare PPO Blue℠	Prior authorization is **not required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

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

HCPCS Codes

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

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT and HCPCS codes above if medical necessity criteria are met:

ICD-10 Diagnosis Codes

ICD-10 CM diagnosis codes:	Code Description
A04.71	Enterocolitis due to Clostridium difficile, recurrent
A04.72	Enterocolitis due to Clostridium difficile, not specified as recurrent

DESCRIPTION

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).

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.[1,] 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.[2,]

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.[3,] The product is made from 33 bacterial isolates developed from culturing stool from a healthy donor.

Summary

Description

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 (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 product that is not commercially available, 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 recurrent *Clostridioides difficile* infection (CDI) refractory to antibiotic therapy who receive fecal microbiota transplantation (FMT) with a commercially available Food and Drug Administration (FDA)-approved product, the evidence includes RCTs and an observational study. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The efficacy of a commercially available rectally administered suspension containing live fecal microbiota spores was evaluated in a phase 3 double-blind, placebo-controlled RCT (PUNCH CD3; N=289), with analysis conducted using a Bayesian hierarchical model that borrowed data from a preceding phase 2b trial (PUNCH CD2; N=134). Both trials included adults with recurrent CDI (1 or more recurrences in PUNCH CD3, and 2 or more recurrences in PUNCH CD2) or a minimum of 2 CDI episodes within the preceding year that led to hospitalization, who received at least 10 consecutive days of standard antibiotic therapy and displayed improvement in CDI symptoms. The rate of treatment success, defined as the absence of CDI within 8 weeks of study treatment, was significantly higher in the group of patients who received rectally administered live fecal microbiota spores as compared to placebo (70.6% vs 57.5%). Additionally, among those patients who achieved treatment success at 8 weeks, more than 90% remained free of CDI recurrence through 6 months. A phase 3, double-blind, placebo-controlled RCT (N=182) evaluated the efficacy of commercially available oral capsules containing live fecal microbiota spores in patients who had at least 2 recurrences within 12 months and who received 10 to 21 consecutive days of standard antibiotic therapy and displayed improvement in CDI symptoms. Results demonstrated that a 3-day course of oral live fecal microbiota spores was more effective than placebo at preventing CDI recurrence within 8 weeks of treatment (12% vs 40%, respectively). In a single-arm, open-label trial evaluating commercially available oral capsules containing live fecal microbiota spores, the CDI recurrence rate at 24 weeks follow-up was 13.7%. Both commercially available therapies were well-tolerated, with the majority of adverse events being mild-to-moderate in severity. 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 randomized controlled trials (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. A small 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 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. One systematic review with meta-analysis involving 19 studies reported that FMT was superior to placebo in improving quality of life through 24 weeks; however, there was no difference in the IBS Severity Scoring System (IBS-SSS) or symptom improvement between FMT and placebo. Conversely, a systematic review with meta-analysis of 9 RCTs found that a single FMT significantly decreased the IBS-SSS score at 1, 3, 6, 24, and 36 months compared to placebo. Another systematic review with meta-analysis reviewed 5 RCTs and reported mixed outcomes for FMT in patients with IBS. 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 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 small study sizes and 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 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.

Policy History

Date	Action
4/2024	Annual policy review. Policy updated with literature review through August 23, 2023; references added. Medically necessary policy statement added for commercially available FDA-approved FMT products, Rebyota and Vowst. Effective 4/1/2024.
1/2023	Clarified coding information. Annual policy review. Description, summary, and references updated. Minor editorial refinements to policy statements; intent unchanged.
1/2022	Annual policy review. Description, summary and references updated. Policy statements unchanged.
4/2021	Annual policy review. First policy statement updated with information from 2017 Infectious Diseases Society of America guidelines for C.diff regarding the number of prior C diff infections before fecal microbiota transplantation is considered (ie, "There have been at least 2 recurrences that are refractory to standard antibiotic treatment"). Effective 4/1/2021.
1/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.

1/2018	Annual policy review. New references added.
10/2017	Clarified coding information.
12/2016	Annual policy review. New references added.
1/2016	Annual policy review. New references added.
6/2015	Annual policy review. New references added.
10/2014	New policy describing medically necessary and investigational indications. Effective 10/1/2014.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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