BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Fecal Microbiota Transplantation

Policy #: 584
Latest Review Date: November 2023
Category: Laboratory

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*

    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after December 22, 2020:

Blue Advantage will treat **the use of fecal microbiota transplantation for treatment of individuals with recurrent Clostridium difficile infection** as a **covered benefit** when:

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

Blue Advantage will treat the **use of fecal microbiota transplantation** as a **non-covered benefit** and as **investigational** in the absence of the condition listed above**.**

Effective for dates of service October 15, 2018 through December 21, 2020:

Blue Advantage will treat **the use of fecal microbiota transplantation for treatment of patients with recurrent Clostridium difficile infection** as a **covered benefit** when:

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

Blue Advantage will treat **the use of fecal microbiota transplantation** as a **non-covered benefit** and as **investigational** in the absence of the condition listed above.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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.

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 though a nasogastric tube or gastroscopy, or 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 ten 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 perform a variety of useful functions including aiding in the digestion of carbohydrates, mediating the synthesis of certain vitamins, repressing 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 fecal microbiota transplantation 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 fecal microbiota transplant 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. A proof of principle study, Perof et al (2013) evaluated a synthetic stool product in two patients with recurrent CDI. The product is made from 33 bacterial isolates developed from culturing stool from a healthy donor.

KEY POINTS:

The most recent literature review was updated through August 23, 2023.

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 a meaningful 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. 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, an 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.

Practice Guidelines and Position Statements

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 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."

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)"
- "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."

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

KEY WORDS:

Fecal microbiota transplant, Donor feces infusion, Intestinal microbiota transplantation, Fecal bacteriotherapy, Fecal transplant, Rebyota™ , Vowst

APPROVED BY GOVERNING BODIES:

In 2022, 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 Food and Drug Administration 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 Food and Drug Administration 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.
- 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, RebyotaTM (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, VowstTM (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.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:

44705	Preparation of fecal microbiota for installation, including assessment of donor specimen
0780T	Instillation of fecal microbiota suspension via rectal enema into lower gastrointestinal tract (Effective 01/01/2023)

HCPCS Codes:

G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen
J1440	Fecal microbiota, live - jslm, 1 ml (Effective 07/01/2023)

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POLICY HISTORY:

Adopted for Blue Advantage, February 2015
Medical Policy Group, February 2015
Medical Policy Group, May 2015
Medical Policy Group, December 2015
Medical Policy Group, November 2016
Medical Policy Group, November 2017
Medical Policy Group, February 2018
Medical Policy Group, October 2018: Reinstated policy effective October 15, 2018.
Medical Policy Group, December 2018
Medical Policy Group, November 2019
Medical Policy Group, December 2020
Medical Policy Group, November 2021
Medical Policy Group, November 2022
Medical Policy Group, December 2022: 2023 Annual Coding Update: Added CPT code 0780T to Current Coding section.
Medical Policy Group, November 2023