



BlueCross BlueShield  
of Alabama

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**Name of Blue Advantage Policy:**  
**Fecal Microbiota Transplantation**

Policy #: 584

Latest Review Date: November 2021

Category: Laboratory

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**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 patients 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.

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### **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 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.

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Effective for dates of service February 26, 2018 through October 14, 2018, refer to LCD L36954.

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### **Effective for dates of service prior to February 26, 2018:**

**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 in the absence of the conditions listed above and as **investigational**.

*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).

### **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, 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 September 29, 2021.

### **Summary of Evidence**

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 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.

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.

## **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

### **APPROVED BY GOVERNING BODIES:**

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 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.

**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
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**HCPCS Codes:**

G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen
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**REFERENCES:**

1. Aldrich AM, Argo T, Koehler TJ, et al. Analysis of treatment outcomes for recurrent Clostridium difficile infections and fecal microbiota transplantation in a pediatric hospital. *Pediatr Infect Dis J.* Mar 29 2018.
2. American College of Gastroenterology (ACG). Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Available online at: [gi.org/guideline/diagnosis-and-management-of-c-difficile-associated-diarrhea-and-colitis/](http://gi.org/guideline/diagnosis-and-management-of-c-difficile-associated-diarrhea-and-colitis/).
3. Anderson JL, Edney RJ, Whelan K. Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease. *Aliment Pharmacol Ther* 2012; 36(6):503-16.
4. Aziz I, Törnblom H, Palsson OS, et al. How the Change in IBS Criteria From Rome III to Rome IV Impacts on Clinical Characteristics and Key Pathophysiological Factors.. *Am. J. Gastroenterol.*, 2018 Jun 9;113(7).
5. Bar-Yoseph H, Carasso S, Shklar S, et al. Oral Capsulized Fecal Microbiota Transplantation for Eradication of Carbapenemase-producing Enterobacteriaceae

- Colonization With a Metagenomic Perspective. *Clin Infect Dis*. Jul 01 2021; 73(1): e166-e175.
6. CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.
  7. Chapman BC, Moore HB, Overbey DM, et al. Fecal microbiota transplant in patients with *Clostridium difficile* infection: A systematic review. *J Trauma Acute Care Surg*. Oct 2016; 81(4):756-764.
  8. Cold F, Kousgaard SJ, Halkjaer SI, et al. Fecal Microbiota Transplantation in the Treatment of Chronic Pouchitis: A Systematic Review. *Microorganisms*. Sep 18 2020; 8(9).
  9. Costello SP, Hughes PA, Waters O, et al. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial. *JAMA*, 2019 Jan 16;321(2).
  10. Crothers JW, Chu ND, Nguyen LTT, et al. Daily, oral FMT for long-term maintenance therapy in ulcerative colitis: results of a single-center, prospective, randomized pilot study. *BMC Gastroenterol*. Jul 08 2021; 21(1): 281.
  11. Drekonja D, Reich J, Gezahegn S, et al. Fecal microbiota transplantation for *Clostridium difficile* infection: a systematic review. *Ann Intern Med*. May 5 2015; 162(9):630-638.
  12. Du C, Luo Y, Walsh S, et al. Oral Fecal Microbiota Transplant Capsules Are Safe and Effective for Recurrent *Clostridioides difficile* Infection: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol*. Apr 01 2021; 55(4): 300-308.
  13. Fang H, Fu L, Li X, et al. Long-term efficacy and safety of monotherapy with a single fresh fecal microbiota transplant for recurrent active ulcerative colitis: a prospective randomized pilot study. *Microb Cell Fact*. Jan 19 2021; 20(1): 18.
  14. Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. *Gastroenterology*. Jun 2021; 160(7): 2496-2508.
  15. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology*. Apr 2020; 158(5): 1450-1461.
  16. Food and Drug Administration (FDA). Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies. July 2013. Available online at: [www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM361393.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM361393.pdf). Accessed October 25, 2017.
  17. Food and Drug Administration (FDA). Fecal Microbiota for Transplantation: New Safety Information - Regarding Additional Protections for Screening Donors for COVID-19 and 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>. Accessed September 29, 2021.

18. Food and Drug Administration (FDA). Fecal Microbiota Transplantation: Safety Communication - Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms. 2019; <https://www.fda.gov/safety/medwatch-safety-alerts-human-medical-products/fecalmicrobiota-transplantation-safety-communication-risk-serious-adverse-reactions-due>. Accessed September 23, 2019.
19. Food and Drug Administration (FDA). Fecal Microbiota Transplantation: Safety Communication - Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms. 2019; <https://www.fda.gov/safety/medwatch-safety-alertshuman-medical-products/fecal-microbiota-transplantation-safety-communication-risk-serious-adverse-reactions-due>. Accessed October 8, 2020.
20. Food and Drug Administration (FDA). Fecal Microbiota Transplantation: Safety Communication - Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms. 2019; <https://www.fda.gov/safety/medwatch-safety-alerts-human-medical-products/fecal-microbiota-transplantation-safety-communication-risk-serious-adverse-reactions-due>. Accessed October 1, 2021.
21. Food and Drug Administration (FDA). Guidance for Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies. 2013; <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-regarding-investigational-new-drug-requirements-use-fecal-microbiota>. Accessed October 8, 2020.
22. Food and Drug Administration (FDA). Guidance for Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies. 2016; <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-regarding-investigational-new-drug-requirements-use-fecal-microbiota-0> Accessed September 28, 2021.
23. Ford AC, Bercik P, Morgan DG, et al. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care.. Gastroenterology, 2013 Sep 3;145(6).
24. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis 2011; 53(10):994- 1002.
25. Guo B, Harstall C, Louie T et al. Systematic review: faecal transplantation for the treatment of Clostridium difficile-associated disease. Aliment Pharmacol Ther 2012; 35(8):865-75.
26. Holster S, Lindqvist CM, Repsilber D, et al. The Effect of Allogenic Versus Autologous Fecal Microbiota Transfer on Symptoms, Visceral Perception and Fecal and Mucosal Microbiota in Irritable Bowel Syndrome: A Randomized Controlled Study.. Clin Transl Gastroenterol, 2019 Apr 23;10(4).
27. Holvoet T, Joossens M, Vazquez-Castellanos JF, et al. Fecal Microbiota Transplantation Reduces Symptoms in Some Patients With Irritable Bowel Syndrome With Predominant Abdominal Bloating: Short- and Long-term Results From a Placebo-Controlled Randomized Trial. Gastroenterology. Jul 15 2020.

28. Holvoet T, Joossens M, Vazquez-Castellanos JF, et al. Fecal Microbiota Transplantation Reduces Symptoms in Some Patients With Irritable Bowel Syndrome With Predominant Abdominal Bloating: Short- and Long-term Results From a Placebo-Controlled Randomized Trial. *Gastroenterology*. Jan 2021; 160(1): 145-157.e8.
29. Huttner BD, de Lastours V, Wassenberg M, et al. A 5-day course of oral antibiotics followed by faecal transplantation to eradicate carriage of multidrug-resistant Enterobacteriaceae: a randomized clinical trial.. *Clin. Microbiol. Infect.*, 2019 Jan 8;25(7).
30. Ianiro G, Eusebi LH, Black CJ, et al. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome.. *Aliment. Pharmacol. Ther.*, 2019 May 29;50(3).
31. IOM (Institute of Medicine). 2011. *Clinical Practice Guidelines We Can Trust*. Washington, DC: The National Academies Press.
32. Johnsen PH, Hilpüsch F, Cavanagh JP, et al. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial.. *Lancet Gastroenterol Hepatol*, 2017 Nov 5;3(1).
33. Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. *Clin Infect Dis*. Sep 07 2021; 73(5): e1029-e1044.
34. Kachrimanidou M, Malisiovas N. Clostridium difficile infection: a comprehensive review. *Crit Rev Microbiol* 2011; 37(3):178-87.
35. Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. *Am J Gastroenterol*. Jun 01 2021; 116(6): 1124-1147.
36. Kelly CR, Khoruts A, Staley C, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent Clostridium difficile infection: a randomized trial. *Ann Intern Med*. Aug 23 2016.
37. Khan MY, Dirweesh A, Khurshid T, et al. Comparing fecal microbiota transplantation to standard-of-care treatment for recurrent Clostridium difficile infection: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol*. Nov 2018;30(11):1309-1317.
38. Kronman MP, Nielson HJ, Adler AL, et al. Fecal microbiota transplantation via nasogastric tube for recurrent clostridium difficile infection in pediatric patients. *J Pediatr Gastroenterol Nutr*. Jan 2015; 60(1):23-26.
39. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. *Am J Gastroenterol*. Jan 01 2021; 116(1): 17-44.
40. Lahtinen P, Jalanka J, Hartikainen A, et al. Randomised clinical trial: faecal microbiota transplantation versus autologous placebo administered via colonoscopy in irritable bowel syndrome. *Aliment Pharmacol Ther*. Jun 2020; 51(12): 1321-1331.
41. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. Dec 2019; 68(Suppl 3): s1-s106.

42. Lee CH, Belanger JE, Kassam Z et al. The outcome and long-term follow-up of 94 patients with recurrent and refractory *Clostridium difficile* infection using single to multiple fecal microbiota transplantation via retention enema. *Eur J Clin Microbiol Infect Dis* 2014.
43. Lee CH, Chai J, Hammond K, et al. Long-term durability and safety of fecal microbiota transplantation for recurrent or refractory *Clostridioides difficile* infection with or without antibiotic exposure. *Eur. J. Clin. Microbiol. Infect. Dis.*, 2019 Jun 6;38(9).
44. Lee CH, Steiner T, Petrof EO, et al. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent *Clostridium difficile* Infection: a randomized clinical trial. *JAMA*. Jan 12 2016; 315(2):142-149.
45. Li Q, Ding X, Liu K, et al. Fecal Microbiota Transplantation for Ulcerative Colitis: The Optimum Timing and Gut Microbiota as Predictors for Long-Term Clinical Outcomes. *Clin Transl Gastroenterol*. Aug 2020; 11(8): e00224.
46. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. Apr 2018; 113(4): 481-517.
47. Madsen AMA, Halkjaer SI, Christensen AH, et al. The effect of faecal microbiota transplantation on abdominal pain, stool frequency, and stool form in patients with moderate-to-severe irritable bowel syndrome: results from a randomised, double-blind, placebo-controlled study. *Scand J Gastroenterol*. Jul 2021; 56(7): 761-769.
48. Mamo Y, Woodworth MH, Wang T, et al. Durability and long-term clinical outcomes of fecal microbiota transplant treatment in patients with recurrent *Clostridium difficile* infection. *Clin Infect Dis*. May 17 2018;66(11):1705-1711.
49. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin. Infect. Dis.*, 2018 Feb 21;66(7).
50. Meighani A, Alimirah M, Ramesh M, et al. Fecal Microbiota Transplantation for *Clostridioides Difficile* Infection in Patients with Chronic Liver Disease. *Int J Hepatol*. 2020; 2020: 1874570.
51. Meighani A, Hart BR, Bourgi K, et al. Outcomes of fecal microbiota transplantation for *Clostridium difficile* infection in patients with inflammatory bowel disease. *Dig Dis Sci*. Oct 2017;62(10):2870-2875.
52. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology*. Jul 2015; 149(1):102-109 e106.
53. Nelson RL, Kelsey P, Leeman H et al. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. *Cochrane Database Syst Rev* 2011; (9):CD004610.
54. Paramsothy S, Paramsothy R, Rubin DT, et al. Faecal microbiota transplantation for inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis*. Oct 1 2017;11(10):1180-1199.
55. Petrof EO, Gloor GB, Vanner SJ et al. Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut. *Microbiome* 2013; 1(1):3.

56. Poylin V, Hawkins AT, Bhama AR, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Clostridioides difficile Infection. Dis Colon Rectum. Jun 01 2021; 64(6): 650-668.
57. Proenca IM, Allegretti JR, Bernardo WM, et al. Fecal microbiota transplantation improves metabolic syndrome parameters: systematic review with meta-analysis based on randomized clinical trials. Nutr Res. Jul 03 2020; 83: 1-14.
58. Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. Aliment Pharmacol Ther. Sep 2017; 46(5):479-493.
59. Ramai D, Zakhia K, Fields PJ, et al. Fecal Microbiota Transplantation (FMT) with Colonoscopy Is Superior to Enema and Nasogastric Tube While Comparable to Capsule for the Treatment of Recurrent Clostridioides difficile Infection: A Systematic Review and Meta-Analysis. Dig Dis Sci. Mar 12 2020.
60. Ramai D, Zakhia K, Fields PJ, et al. Fecal Microbiota Transplantation (FMT) with Colonoscopy Is Superior to Enema and Nasogastric Tube While Comparable to Capsule for the Treatment of Recurrent Clostridioides difficile Infection: A Systematic Review and Meta-Analysis. Dig Dis Sci. Feb 2021; 66(2): 369-380.
61. Rokkas T, Gisbert JP, Gasbarrini A, et al. A network meta-analysis of randomized controlled trials exploring the role of fecal microbiota transplantation in recurrent Clostridium difficile infection. United European Gastroenterol J. Oct 2019; 7(8): 1051-1063.
62. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology. Jul 2015; 149(1):110-118 e114.
63. Rossen NG, MacDonald JK, de Vries EM, et al. Fecal microbiota transplantation as novel therapy in gastroenterology: A systematic review. World J Gastroenterol. May 7 2015; 21(17):5359-5371.
64. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults.. Am. J. Gastroenterol., 2019 Mar 7;114(3).
65. Saha S, Tariq R, Tosh PK, et al. Faecal microbiota transplantation for eradicating carriage of multidrug-resistant organisms: a systematic review. Clin Microbiol Infect. Aug 2019; 25(8): 958-963.
66. Sha S, Liang J, Chen M, et al. Systematic review: faecal microbiota transplantation therapy for digestive and nondigestive disorders in adults and children. Aliment Pharmacol Ther. May 2014; 39(10):1003-1032.
67. Sofi AA, Silverman AL, Khuder S et al. Relationship of symptom duration and fecal bacteriotherapy in Clostridium difficile infection-pooled data analysis and a systematic review. Scand J Gastroenterol 2013; 48(3):266-73.
68. Sokol H, Landman C, Seksik P, et al. Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. Microbiome. Feb 03 2020; 8(1): 12.

69. Sood A, Mahajan R, Singh A, et al. Role of Faecal Microbiota Transplantation for Maintenance of Remission in Patients With Ulcerative Colitis: A Pilot Study. *J Crohns Colitis*. Sep 27 2019; 13(10): 1311-1317.
70. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. Apr 2013;108(4):478-498; quiz 499.
71. Tariq R, Pardi DS, Bartlett MG, et al. Low Cure Rates in Controlled Trials of Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection: A Systematic Review and Meta-analysis. *Clin. Infect. Dis.*, 2019 Apr 9;68(8).
72. van Nood E, Vrieze A, Nieuwdorp M et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; 368(5):407-15.
73. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology*. Oct 2012; 143(4):913-916 e917.
74. Wang S, Xu M, Wang W, et al. Systematic review: adverse events of fecal microbiota transplantation. *PLoS One*. 2016; 11(8):e0161174.
75. Youngster I, Sauk J, Pindar C et al. Fecal microbiota transplant for relapsing *clostridium difficile* infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. *Clin Infect Dis* 2014.
76. Zhou HY, Guo B, Lufumpa E, et al. Comparative of the Effectiveness and Safety of Biological Agents, Tofacitinib, and Fecal Microbiota Transplantation in Ulcerative Colitis: Systematic Review and Network Meta-Analysis. *Immunol Invest*. Feb 02 2020: 1-15.
77. Zhou HY, Guo B, Lufumpa E, et al. Comparative of the Effectiveness and Safety of Biological Agents, Tofacitinib, and Fecal Microbiota Transplantation in Ulcerative Colitis: Systematic Review and Network Meta-Analysis. *Immunol Invest*. May 2021; 50(4): 323-337.

## **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

*This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.*