Fecal Microbiota Transplantation
Clinical Coverage Criteria

Description

Clostridioides (formerly Clostridium) difficile infection occurs when the bacterium produces toxin that causes diarrhea and inflammation of the colon. These infections range in severity from mild symptoms to life threating colitis. Recurrent *C. difficile* infection is defined as an episode of *C. difficile* infection that occurs eight weeks or less after the initial episode that resolved with or without therapy. Oral antibiotics are first line treatments for *C. difficile* infection. Published data suggest that the use of fecal microbiota to restore intestinal flora may be an effective therapy in the management of refractory *C. difficile* infection. Patients experiencing 2 or more recurrences of *C. difficile* infection may be candidates for fecal microbiota transplantation to prevent further recurrences.

Policy

This Policy applies to the following Fallon Health products:

☒ Fallon Medicare Plus, Fallon Medicare Plus Central (Medicare Advantage)

☒ MassHealth ACO

☒ NaviCare HMO SNP (Dual Eligible Medicare Advantage and MassHealth)

☒ NaviCare SCO (MassHealth-only)

☒ PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)

☒ Community Care (Commercial/Exchange)

Prior authorization is not required. Refer to Coding section for ICD-10-Diagnosis codes that support medical necessity for plan members meeting criteria described below.

Medicare Advantage

Fallon Health complies with CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations for Medicare Advantage members. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health may create internal coverage criteria under specific circumstances described at § 422.101(b)(6)(i) and (ii).

Medicare statutes and regulations do not have coverage criteria for fecal microbiota transplantation. Medicare does not have an NCD for fecal microbiota transplantation. National Government Services, Inc., the Part A/B Medicare Administrative Contractor (MAC) with jurisdiction in our service area, does not have an LCD for fecal microbiota transplantation (MCD search 03/22/2024), therefore Fallon Health Clinical Coverage Criteria are applicable.

MassHealth

Fallon Health follows Medical Necessity Guidelines published by MassHealth when making medical necessity determinations for MassHealth members. In the absence of Medical Necessity Guidelines published by MassHealth, Fallon Health may create clinical coverage criteria in accordance with the definition of Medical Necessity in 130 CMR 450.204.

MassHealth does not have Guidelines for Medical Necessity Determination for fecal microbiota transplantation, therefore, Fallon Health Clinical Coverage Criteria are applicable (MassHealth website search 02/25/2024)

NaviCare HMO SNP, NaviCare SCO
For plan members enrolled in NaviCare, Fallon Health first follow's CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, or if the NaviCare member does not meet coverage criteria in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health then follows Medical Necessity Guidelines published by MassHealth when making necessity determinations for NaviCare members.

PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
Each PACE plan member is assigned to an Interdisciplinary Team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Fallon Health Clinical Coverage Criteria

Fallon Health considers fecal microbiota transplantation (G0455) medically necessary for the prevention of recurrent *Clostridioides* (formerly Clostridium) *difficile* infection when the following criteria are met:

1. The member has had 3 or more recurrent episodes of *C. difficile* infection confirmed by positive stool tests, AND
2. The episodes are refractory to appropriate antibiotic therapy regimens, including at least one regimen of tapered and pulsed vancomycin.

A second fecal microbiota transplantation with donor stool is covered for those plan member's who relapse after initial FMT provided the member completes at least a 10-day course of vancomycin before repeating the procedure (Kelly et al., 2016; Allegretti et al., 2021).

Exclusions

Fecal microbiota transplantation is considered experimental or investigational for all other indications, including but not limited to Crohn's disease and inflammatory bowel disease. If a procedure lacks scientific evidence regarding safety and efficacy because it is investigational or experimental, the service is noncovered as not reasonable and necessary or not medically necessary to treat illness or injury.

Evidence Summary

Food and Drug Administration
The Food and Drug Administration (FDA) has developed guidance to ensure that patients with *C. difficile* infection not responding to standard therapies have access to fecal microbiota for transplantation, while addressing and controlling the risks that centralized manufacturing in stool banks presents to subjects: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies (November 2022). The FDA intends to exercise enforcement discretion with respect to applicable Investigational New Drug requirements when the fecal microbiota transplantation product is not obtained from a stool bank and where requirements in section II of this guidance are followed.

Presently, there are two FDA-approved fecal microbiota products:

- REBYOTA (fecal microbiota, live – jslm) (Manufactured for Ferring Pharmaceuticals, by Rebiotix, Inc., Roseville, MN 55113) was approved by the FDA for the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older following antibiotic treatment for recurrent CDI on November 30, 2022. Rebyota is administered as a single dose rectal enema within 24 to 72 hours after completion of antibiotic therapy. Rebyota is not indicated for treatment of CDI.
- VOWST (fecal microbiota spores, live-brpk) (Manufactured by Seres Therapeutics Inc.) was approved by the FDA for the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI on April 26, 2023. For oral administration only. VOWST is not indicated for treatment of CDI.

Fecal microbiota donor material is also produced at OpenBiome (Cambridge, MA) for use in clinical research studies (Chen et al., 2021).

Additionally, stool from a healthy donor may be used (patient-selected donor model).

The FDA has published several Safety Alerts related to the use of fecal microbiota transplantation. Two alerts document transmission of pathogenic *Escherichia coli* from donor to fecal microbiota transplantation recipients, some of whom became ill and some of whom died. As explained in the safety alerts, FDA suspects the infections were due to transmission of these pathogenic organisms from the fecal microbiota transplantation product. See Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms (March 12, 2020); Update to March 12, 2020 Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms (March 13, 2020).

Early Studies

Patients who have failed to resolve recurrent *C. difficile* infection despite repeated antibiotic treatment attempts present a particularly difficult challenge. Clinical investigations of patients with recurrent *C. difficile* infection have shown significant disruption of the intestinal microbiome diversity as well as relative bacterial population numbers. Instillation of processed stool collected from a healthy donor into the intestinal tract of patients with recurrent *C. difficile* infection has been used with a high degree of success to correct the intestinal dysbiosis brought about by repeated courses of antibiotic administration (Aas et al., 2003, Bakken, 2009, Gough and Shaikh, 2011). Anecdotal treatment success rates of fecal microbiota transplantation for recurrent *C. difficile* infection have been high regardless of route of instillation of feces, and have ranged between 77% and 94% with administration via the proximal small bowel (Aas et al., 2003, MacConnachie et al, 2009); the highest success rates (80%–100%) have been associated with instillation of feces via the colon (Gough and Shaikh, 2011, Brandt et al., 2012, Hamilton et al., 2012, Jorup-Rönström et al., 2012, Mattila et al., 2012).

Randomized Controlled Trials

Despite the large number of anecdotal reports that have consistently demonstrated high efficacy of fecal microbiota transplantation, the first prospective randomized clinical trial that compared the outcome of standard antibiotic therapy to fecal microbiota transplantation was published in 2013 (van Nood et al., 2013). In this unblinded trial, van Nood and collaborators randomly assigned 43 patients with ≥ 2 recurrent episodes of *C. difficile* infection to receive either a standard 14-day course of oral vancomycin (13 patients), vancomycin with bowel lavage (13 patients), or a 4-day course of vancomycin followed by bowel lavage and subsequent FMT infusion administered through a nasoduodenal tube (17 patients). The primary endpoint was initial response without relapse for 10 weeks after completion of therapy. The investigation was terminated early after interim analysis, due to the marked difference in treatment outcomes. Thirteen of the 16 (81%) patients in the FMT arm had a sustained resolution of diarrhea after the first fecal infusion; only 7 of the 26 (27%) patients who were treated with vancomycin resolved their *C. difficile* infection ($p < 0.001$).

Four additional randomized trials of fecal microbiota transplantation have been published through 2016. One of these trials compared fecal microbiota transplantation to antibiotic treatment (Cammarota et al., 2015) and the other 3 compared various refinements of the fecal microbiota transplantation product (Lee et al., 2016), delivery of the product (Youngster et al., 2014), or fecal microbiota transplantation to autologous fecal microbiota transplantation (Kelly et al., 2016). In general, the reported efficacy of fecal microbiota transplantation is lower in most randomized trials than in nonrandomized reports. The largest of these randomized trials (Kelly et al., 2016) reported an efficacy of approximately 50% for one fecal microbiota transplantation delivered by enema, which increased to 75% for 2 fecal microbiota transplantation administrations and approximately 90% for >2 fecal microbiota transplantation administrations. Patient selection, proximity to recurrent *C. difficile* infection episode, and antibiotic treatment prior to fecal microbiota transplantation all likely influence response to fecal microbiota transplantation.

Fecal Microbiota Re-Transplantation
In a multicenter, retrospective review of 540 patients that underwent at least one fecal microbiota transplantation, 432 patients had success following the first transplantation and 108 had documented failure (25%). Among those who failed the first transplantation, 63 patients received a second transplantation, of which 36 achieved cure and 24 had documented failure after the second transplantation. The second failure rate was 4.8%. Risk factors for second failure included inpatient status, the presence of pseudomembranes, and immunocompromised state at the time of first transplantation (Allegretti et al., 2021).

Fecal Microbiota Transplantation in Immunocompromised Patients
Kelly et al., 2014, performed a multicenter retrospective case series on the use of fecal microbiota transplantation in immunocompromised patients with *C. difficile* infection that was recurrent, refractory, or severe. Cases included adult (75) and pediatric (5) patients treated with fecal microbiota transplantation for recurrent (55%), refractory (11%), and severe and/or overlap of recurrent/refractory and severe *C. difficile* infection (34%). In all, 79% were outpatients at the time of fecal microbiota transplantation. The mean follow-up period between fecal microbiota transplantation and data collection was 11 months (range 3-46 months). Reasons for immunocompromise included: HIV/AIDS (3), solid organ transplant (19), oncologic condition (7), immunosuppressive therapy for inflammatory bowel disease (IBD; 36), and other medical conditions/medications (15). The *C. difficile* infection cure rate after a single fecal microbiota transplantation was 78%, with 62 patients suffering no recurrence at least 12 weeks post fecal microbiota transplantation. Twelve patients underwent repeat fecal microbiota transplantation, of whom eight had no further *C. difficile* infection. Thus, the overall cure rate was 89%. Twelve patients (15%) had any serious adverse event within 12 weeks post fecal microbiota transplantation, of which 10 were hospitalizations. Two deaths occurred within 12 weeks of fecal microbiota transplantation, one of which was the result of aspiration during sedation for fecal microbiota transplantation administered via colonoscopy; the other was unrelated. None suffered infections definitely related to fecal microbiota transplantation, but two patients developed unrelated infections and five had self-limited diarrheal illness in which no causal organism was identified (Kelly et al,. 2014).

Fecal Microbiota Transplantation in Patients with Severe, Refractory *C. difficile* infection, IBD and Other Conditions
There are limited data on fecal microbiota transplantation administration in patients with severe, refractory (Weingarden et al., 2013, Fischer et al., 2015). Fecal microbiota transplantation has also been used for treating recurrent *C. difficile* infection in patients with underlying IBD, although it appears to be less effective for this population compared to those without IBD (Khoruts et al., 2016, Tariq et al., 2020, Allegretti et al., 2021) and flares of underlying disease activity have been reported following fecal microbiota transplantation for recurrent *C. difficile* infection in patients with IBD (Khoruts et al., 2016, De Leon et al., 2013, Fischer et al., 2016).

Fecal Microbiota Transplantation in Pediatric Patients

At present, robust data examining the effectiveness of fecal microbiota transplantation for pediatric patients are lacking. Limited evidence from case reports and case series in pediatric patients suggests that FMT via nasogastric tube or colonoscopy can be effective in children with recurrent *C. difficile* infection who have failed standard antibiotic therapy, with follow-up periods up to 16 months (Russell et al., 2010, Walia et al., 2014). In most reported cases, fecal sample donation was from the child's mother or father (Walia et al., 2014). Despite limited pediatric data, a survey of pediatric infectious diseases physicians revealed that 18% of respondents who reported using alternative therapies for C. difficile infection had recommended fecal microbiota transplantation, most commonly for the treatment of a third or later recurrence (Sammons et al., 2014). The potential benefits of fecal microbiota transplantation must be balanced against theoretical risks. As described above, instillation of donor stool typically requires use of nasogastric tube or colonoscopy, which may carry procedure-related risks. In addition, use of donor stool introduces the potential for transmission of resistant organisms and blood-borne pathogens, necessitating donor-screening protocols.

Complications
Reported infectious complications directly attributed to the instillation of donor feces has so far been limited to 2 patients who developed norovirus gastroenteritis after fecal microbiota transplantation for treatment of *C. difficile* infection despite use of asymptomatic donors and lack of sick contacts (Schwartz et al., 2013).

Physical complications from the fecal microbiota transplantation instillation procedure (upper gastrointestinal bleed after nasogastric tube insertion, colon perforation during colonoscopy) has been occasionally reported and may occur with the same frequency as when these procedures are performed for gastrointestinal illnesses other than recurrent *C. difficile* infection. Potential unintended long-term infectious and noninfectious consequences of fecal microbiota transplantation are still unknown in the absence of large-scale controlled trials with sufficient follow-up.

Clinical Practice Guidelines
Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.

IDSA and SHEA Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update
A panel of experts was convened by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) to update the 2010 clinical practice guideline on *Clostridium (C.) difficile* infection in adults. The update, which has incorporated recommendations for children (following the adult recommendations for epidemiology, diagnosis, and treatment), includes significant changes in the management of this infection and reflects the evolving controversy over best methods for diagnosis. The panel followed a process used in the development of other IDSA guidelines, which included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system. A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of the guidelines. The extent to which these guidelines can be implemented is impacted by the size of the institution and the resources, both financial and laboratory, available in the particular clinical setting.

The 2017 IDSA/SHEA Guidelines Update recommends testing for *C. difficile* infection in patients with unexplained and new onset ≥ 3 unformed stools in 24 hours. There are a variety of available options for laboratory testing to support the diagnosis of *C. difficile* infection, and these are well described in recent reviews (Burnham and Carroll, 2013; Wilcox, 2012). In brief, laboratory tests detect either the organism or one or both of its major toxins (A and B) directly in stool. If patients are screened carefully for clinical symptoms likely associated with *C. difficile* infection (at least 3

loose or unformed stools in ≤24 hours with history of antibiotic exposure), then a highly sensitive test such as a nucleic acid amplification test (NAAT) alone or multistep algorithm (i.e., glutamate dehydrogenase (GDH) plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) is recommended. A 2- or 3-stage approach increases the positive predictive value (PPV) vs one-stage testing. Use of multiple antibiotics (mean number used, 4.2 vs 1.4 antibiotics) is an important risk factor for developing *C. difficile* infection and the incidence of *C. difficile* infection increases with the number of antibiotics prescribed (McDonald et al., 2018).

- The 2017 IDSA/SHEA Guideline recommends fecal microbiota transplantation for patients with multiple recurrences of *C. difficile* infection who have failed appropriate antibiotic treatments (strong recommendation, moderate quality of evidence). The guideline goes on to state: "Although there are no data to indicate how many antibiotic treatments should be attempted before referral for fecal microbiota transplantation, the opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 *C. difficile* infection episodes) should be tried (p. e36)."

- Fecal microbiota transplantation may be considered for pediatric patients with multiple recurrences of *C. difficile* infection following standard antibiotic treatments *(*weak recommendation, very low quality of evidence*)*.

IDSA and SHEA Clinical Practice Guidelines for the Management of Clostridioides difficile Infection in Adults: 2021 Update
Since publication of the 2017 Clinical Practice Guidelines for *Clostridioides* (formerly *Clostridium*) *difficile* infection, new relevant evidence has emerged for treatment options in the management of *C. difficile* infection in adults. The previous guidelines included pediatric treatment recommendations, but the scope of this focused update is restricted to adults and includes new data for fidaxomicin and for bezlotoxumab, a monoclonal antibody targeting toxin B produced by *C. difficile* infection. Both of these agents have increased clinical efficacy and other advantages over older agents, but implementation may be challenging because of initial monetary cost and logistics (Johnson et al., 2021).

While the previous recommendation for use of fecal microbiota transplantation has not been changed, the Guidelines note that 3 separate safety alerts have been published by the U.S. Food and Drug Administration (FDA) since June of 2019, which outline adverse events or potential adverse events among recipients of fecal microbiota transplantation. Two alerts document transmission of pathogenic *Escherichia coli* from donor to fecal microbiota transplantation recipients, some of whom became ill and some of whom died. The other alert concerns the potential for transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As a reminder, fecal microbiota transplantation is recommended only for patients with multiple recurrences of *C. difficile* infection who have failed appropriate antibiotic treatments and where appropriate screening of donor and donor fecal specimens has been performed, in accordance with these newer FDA recommendations.

This focused update includes 3 new recommendations for the treatment of *C. difficile* infection in adults, 2 of which modify our previous recommendations on treatment of an initial *C. difficile* infection episode and treatment of a first recurrent *C. difficile* infection episode. The other recommendation is a new recommendation for use of an adjunctive treatment agent for *C. difficile* infection.

All recommendations were labeled as either “strong” or “conditional” according to the GRADE approach. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations. The latter recognizes that different choices will be appropriate for different patients and that clinicians must help each patient to arrive at a management decision consistent with their own values and preferences.

- For patients with an initial *C. difficile* infection episode, the Guidelines suggest using fidaxomicin (200 mg given twice daily for 10 days) rather than a standard course of vancomycin (125 mg given 4 times daily by mouth for 10 days) (*conditional recommendation, moderate certainty of evidence*). Comment: This recommendation places a high value in the beneficial effects and safety of fidaxomicin, but its implementation depends upon available resources. Vancomycin remains an acceptable alternative.

- In patients with recurrent *C. difficile* infection episodes, the Guidelines suggest fidaxomicin (standard or extended-pulsed regimen) (200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days) rather than a standard course of vancomycin (125 mg given 4 times daily by mouth for 10 days) (conditional recommendation, low certainty evidence). Comment: Vancomycin in a tapered and pulsed regimen or vancomycin as a standard course are acceptable alternatives for a first *C. difficile* infection recurrence. For patients with multiple recurrences, vancomycin in a tapered and pulsed regimen, vancomycin followed by rifaximin, and fecal microbiota transplantation are options in addition to fidaxomicin.

- For patients with a recurrent *C. difficile* infection episode within the last 6 months, the Guidelines suggest using bezlotoxumab as a co-intervention along with standard-of-care antibiotics rather than standard of care antibiotics alone (conditional recommendation, very low certainty of evidence). Comment: This recommendation places a high value on potential clinical benefits, but implementation is often limited by feasibility considerations. In settings where logistics is not an issue, patients with a primary *C. difficile* infection episode and other risk factors for *C. difficile* infection recurrence (such as age ≥65 years, immunocompromised host [per history or use of immunosuppressive therapy], and severe *C. difficile* infection on presentation) may particularly benefit from receiving bezlotoxumab. Data on the use of bezlotoxumab when fidaxomicin is used as the SOC antibiotic are limited. The FDA warns that “in patients with a history of congestive heart failure (CHF), bezlotoxumab should be reserved for use when the benefit outweighs the risk.”

American Gastroenterological Association Fecal Microbiota-Based Therapies for Select Gastrointestinal Diseases (published February 21, 2024)
The American Gastroenterological Association (AGA) released the first comprehensive evidence-based guideline on the use of fecal microbiota-based therapies for gastrointestinal disease, recommending fecal microbiota transplantation in most cases of recurrent *C. difficile* infection (Peery et al., 2024).

Specifically, the guideline recommends the use of fecal microbiota transplantation in patients with recurrent *C. difficile* infection at high risk of recurrence following standard-of-care antibiotics and in hospitalized patients with severe *C. difficile* infection after standard-of-care antibiotics if there is no improvement. Of note, the AGA does not recommend fecal microbiota transplantation therapies for inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS).

The guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework to prioritize clinical questions, identify patient-centered outcomes, and conduct an evidence synthesis. The guideline panel comprised 3 members of the AGA guideline committee, a senior methodologist, a junior methodologist, and 3 experts in fecal microbiota-based therapies. Of note, a patient representative also participated in the development of recommendations.

The guideline panel identified 7 clinically relevant questions to address the use of fecal microbiota-based therapies in adults for the management of recurrent *C. difficile* infection or conventional fecal microbiota transplantation for severe to fulminant *C. difficile* infection, IBD, and IBS. The clinical questions were formulated using the PICO format, and the panel selected desirable and undesirable patient-important outcomes and summarized the evidence for each of the questions.

Randomized controlled trials were used to address PICO questions, but investigators supplemented with observational comparative studies and single-arm observational studies as needed when other evidence was not available. The intervention of interest was the administration of fecal microbiota-based therapies. Accordingly, investigators considered studies with conventional fecal microbiota transplantation using unrelated and minimally manipulated donor stool, FDA-approved fecal microbiota, live-jslm, FDA-approved fecal microbiota spores, live-brpk, and the investigational product CP101.

Investigators conducted a literature search on electronic databases including Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, MEDLINE, and Embase, also searching for ongoing trials at www.clinicaltrials.gov. Each relevant title and abstract underwent screening, and studies that met the criteria for inclusion underwent full-text review for final inclusion for evidence synthesis. In total, 66 studies were included in the review to inform the clinical guidance.

Using the Evidence-to-Decision framework, the guideline panel developed 7 recommendations for the use of fecal microbiota-based therapies in specific gastrointestinal conditions and provided implementation considerations for clinical practice. The guideline recommendations are intended to provide the basis for rational informed decision-making for patients and healthcare professionals using fecal microbiota-based therapies for adults with recurrent *C. difficile* infection or conventional fecal microbiota transplantation for severe to fulminant *C. difficile* infection, IBD, and IBS.

In immunocompetent adults with recurrent *C. difficile* infection, the guideline suggests select use of fecal microbiota-based therapies after completion of standard-of-care antibiotics to prevent recurrence. Additionally, the AGA recommends select use of conventional fecal microbiota transplantation in mildly or moderately immunocompromised adults with recurrent *C. difficile* infection as well as in adults hospitalized with severe or fulminant *C. difficile* infection not responding to standard-of-care antibiotics.

In severely immunocompromised adults, the AGA does not recommend the use of any fecal microbiota-based therapies to prevent recurrent *C. difficile* infection. The guideline also suggests against the use of conventional fecal microbiota transplantation as treatment for IBD or IBS, except in the context of clinical trials.

Recommendations

1. In immunocompetent adults with recurrent *C. difficile* infection, the AGA suggests the use of fecal microbiota-based therapies upon completion of standard-of-care antibiotics over no fecal microbiota-based therapies (conditional recommendation, low certainty evidence).

2. In mildly or moderately immunocompromised adults with recurrent *C. difficile* infection, the AGA suggests the use of conventional fecal microbiota transplantation upon completion of standard-of-care antibiotics over no fecal microbiota transplantation (conditional recommendation, very low certainty evidence). In severely immunocompromised adults with recurrent *C. difficile* infection, the AGA suggests against the use of fecal microbiota-based therapies upon completion of standard-of-care antibiotics over no fecal microbiota-based therapies (conditional recommendation, very low certainty evidence).

3. In adults hospitalized with severe or fulminant *C. difficile* infection not responding to antimicrobial therapy, the AGA suggests the use of conventional fecal microbiota transplantation over no fecal microbiota transplantation (conditional recommendation, very low certainty evidence).

4. In adults with ulcerative colitis, the AGA suggests against the use of conventional fecal microbiota transplantation except in the context of clinical trials (conditional recommendation, very low certainty of evidence).

5. In adults with Crohn's disease, the AGA suggests against the use of conventional fecal microbiota transplantation except in the context of a clinical trial (conditional recommendation, very low certainty of evidence).

6. In adults with pouchitis, the AGA suggests against the use of conventional fecal microbiota transplantation except in the context of clinical trials (conditional recommendation, very low certainty of evidence).

7. In adults with irritable bowel syndrome, the AGA suggests against the use of conventional fecal microbiota transplantation except in the context of clinical trials (conditional recommendation, very low certainty of evidence).

The American Society of Colon and Rectal Surgeons (ASCRS) Clinical Practice Guidelines for the Management of *Clostridioides difficile* Infection
The ASCRS Guideline (Poylin et al., 2021) recommends fecal bacteriotherapy (e.g., intestinal microbiota transplantation) for patients with recurrent or refractory C. difficile infection should typically be considered for if conventional measures, including appropriate antibiotic treatment, have failed. Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Patient with 3 or more *C. difficile* infection episodes can be managed with a vancomycin tapered and pulsed course or fidaxomicin followed by a microbiome-based therapy such as fecal microbiota transplantation. Randomized, controlled trials, systematic reviews, and meta-analyses suggest that patients with recurrent or refractory *C. difficile* infection in whom medical treatment has failed should be considered for fecal transplantation. In general, conventional antibiotic treatment should be used for at least 2 recurrences (i.e., 3 *C. difficile* infection episodes) before offering fecal microbiota transplantation. In terms of the technical aspects involved, randomized, controlled trials have shown similar *C. difficile* infection cure rates after fecal transplants performed with fresh and frozen fecal samples. Given the significant heterogeneity with which fecal transplants have been conducted clinically, standardized products for microbiome-based therapies have been commercialized. Although a number of methods of administration have been described, including using a nasogastric tube or enema, the most common transplant delivery route is via colonoscopy; however, oral capsules were found to be noninferior to colonoscopy delivery for preventing recurrent infection. Overall success rates for fecal transplantation, regardless of the delivery mode, are reported to be between 60% and 90% after a single treatment.

The American College of Gastroenterology (ACG) Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides Difficile* Infections
Published by Kelly et al., 2021, this guideline makes the following recommendations:

- "We suggest fecal microbiota transplantation be considered for patients with severe and fulminant *C. difficile* infection 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 *C. difficile* infection be treated with fecal microbiota transplantation to prevent further recurrences (strong recommendation, moderate quality of evidence)."

- "We recommend fecal microbiota transplantation be delivered through colonoscopy (strong recommendation, moderate quality of evidence) or capsules (strong recommendation, moderate quality of evidence) for treatment of *C. difficile* infection; we suggest delivery by

enema if other methods are unavailable (conditional recommendation, low quality of evidence)."

- "We suggest repeat fecal microbiota transplantation for patients experiencing a recurrence of *C. difficile* infection within 8 weeks of an initial fecal microbiota transplantation (conditional recommendation, very low quality of evidence)."

- "FMT should be considered for recurrent *C. difficile* infection in patients with IBD (strong recommendation, very low quality of evidence)."

Patients should be evaluated again for late failure between 4 and 8 weeks post fecal microbiota transplantation. If fecal microbiota transplantation failure is confirmed, repeat fecal microbiota transplantation should be offered. In a large cohort study that assessed multiple fecal microbiota transplantation failures, less than 5% of patients failed a second fecal microbiota transplantation (Allegretti et al., 2021). Once fecal microbiota transplantation failure is confirmed, anti- *C. difficile* infection antibiotics should be restarted to control symptoms before repeating fecal microbiota transplantation (van Nood et al., 2013). Reasons for failure, such as treatment with concomitant non *C. difficile* infection antibiotics, should be considered. Colonoscopic delivery is the preferred route for those who fail to achieve cure with fecal microbiota transplantation through enema or encapsulated formulations. For patients who do not want or cannot undergo repeat fecal microbiota transplantation, alternative treatment options include prolonged or indefinite treatment with vancomycin; this can usually be tapered down to a single daily dose.

American College of Gastroenterology (ACG) clinical guideline: Management of Irritable Bowel Syndrome

This ACG guideline published by Lacy et al., 2021, recommended against the use of fecal transplant for the treatment of global IBS symptoms (strong recommendation; very low quality of evidence).

American College of Gastroenterology (ACG) Clinical Guideline: Ulcerative Colitis in Adults

In 2019, the ACG published guidelines on the management of adults with ulcerative colitis (UC), noting that "fecal microbiota transplantation (FMT) requires more study and clarification of treatment before use as therapy for UC (Rubin et al. 2019).

Analysis of Evidence (Rationale for Determination)

IDSA/SHEA Guidelines recommend fecal microbiota transplantation for patients with multiple recurrences of *C. difficile* infection who have failed appropriate antibiotic treatments (strong recommendation, moderate quality of evidence). Although there are no data to indicate how many antibiotic treatments should be attempted before referral for fecal microbiota transplantation, the opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation. Guidelines published by the American Gastroenterological Association, the American Society of Colon and Rectal Surgeons and the American College of Gastroenterology also recommend fecal microbiota transplantation for prevention of *C. difficile* infection.

Fecal microbiota transplantation has been well accepted by patients and represents a viable alternative treatment approach to an increasing clinical problem. Judged by the published literature, fecal microbiota transplantation appears to be safe in the short term and mild to moderate post-treatment adverse events are for the most part self-limited. The FDA issued a Safety Alert about four patients who developed Shigatoxin-producing *Escherichia coli* infection from stool prepared from a single donor. Two of those patients died.

At this time, fecal microbiota transplantation is not recommended for the prevention or treatment of any other condition, including IBD or ulcerative colitis. A large number of clinical trials

investigating the use of fecal microbiota transplantation are underway. A search of the clinicaltrials.gov database returned 118 actively recruiting studies investigating the use of fecal microbiota transplantation for the treatment of conditions such as Parkinson's Disease, Crohn's Disease, Multidrug-Resistant Organisms, liver failure, IBS, ulcerative colitis, and post allogeneic transplantation.

Coding

The following codes are included below for informational purposes only; inclusion of a code does not constitute or imply coverage.

CPT/HCPCS Codes

Code	Description
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen
J1440	Fecal microbiota, live - jslm, 1 mL billed as 150 mL
0780T	Instillation of fecal microbiota suspension via rectal enema into lower gastrointestinal tract

CPT 44705 is not valid for Medicare purposes and should not be used to report preparation of fecal microbiota for instillation. CMS created HCPCS code G0455 effective January 1, 2013 (CMS-1600-FC). This code describes the preparation and instillation of fecal microbiota by any method, including assessment of donor specimen, and doesn't involve the administration of any FDA approved drug. Payment for the preparation of the donor specimen is only made if the specimen is ultimately used for the treatment of a member because the Plan does not pay for services not directly related to the diagnosis and treatment of a plan member.

CPT 44705 is nonpayable per MassHealth (Transmittal Letter AOH-49, effective 01/01/2021; Transmittal Letter PHY-162; effective 11/01/2021). MassHealth covers HCPCS code G0455 for preparation and instillation of fecal microbiota by any method.

Effective for dates of service on or after September 1, 2022, CPT 44705 will deny vendor liable for all plan members. HCPCS code G0455 may be used to report fecal microbiota preparation and instillation by any method, including assessment of donor specimen, for all plan members. Effective for dates of service on or after June 1, 2022, G0455 will not require prior authorization.

Effective for claims with dates of service on or after July 1, 2023, providers should bill Rebyota fecal microbiota, live-jslm (HCPCS code J1440), with fecal microbiota transplantation (FMT) procedure (HCPCS code 0780T) for Medicare and Community Care members. Both J1440 and 0780T must be reported on the same claim. J1440 has pass through status on the OPPS and ASC fee schedule (MLN Matters: MM13210; Related Change Request: CR13210).

ICD10 A04.71 (Enterocolitis due to Clostridium difficile, recurrent) or A04.72 (Enterocolitis due to Clostridium difficile, not specified as recurrent) are the only diagnosis codes that will be considered for coverage.

ICD-10 Diagnosis Codes

Code	Description
A04.71	Enterocolitis due to Clostridium difficile, recurrent
A04.72	Enterocolitis due to Clostridium difficile, not specified as recurrent

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Policy history

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Approval(s):	Technology Assessment Committee: 05/24/2017 (approved new policy), 05/15/2018 (updated references), 05/22/2019 (updated references); 07/22/2020 (updated coverage criteria to require at least one regimen of tapered and pulsed vancomycin; updated coding and references), 06/25/2021 (Added clarifying language related to Medicare Advantage, NaviCare and PACE under policy section), 07/28/2021 (annual review), 03/22/2022 (annual review; updated Coding section), 03/26/2024 (annual review; criteria unchanged; updated to include Evidence Summary and Analysis of Evidence (Rationale for Determination)).

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully-insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans.