MEDICAL POLICY	Fecal Microbiota Transplantation
Effective Date: 6/1/2021  6/1/2021 Medical Officer Date	Medical Policy Number: 126 Technology Assessment Committee Approved Date: 3/13; 7/13; 7/14; 6/15; 11/15; 7/16; 8/16 Medical Policy Committee Approved Date: 12/15; 9/17; 7/18; 8/19; 3/2020; 05/2021

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

I. Fecal microbiota transplantation may be considered **medically necessary and covered** for the treatment of Clostridioides difficile (formerly known as Clostridium) (C. difficile) infection when **all** of the following criteria are met (A. - C.):

   A. The patient has had at least two episodes (initial episode plus one or more recurrences) of C. difficile infection that have not responded with appropriate treatment with antibiotics; **and**
   B. Testing confirms diagnosis of C. difficile infection by **both** of the following (1. and 2.):
      1. Recurrent diarrhea (>3 unformed stools in ≤24 hours); **and**
      2. Either of the following:
         a. Stool sample positive for C. difficile or its toxins; **or**
         b. Colonoscopic or histopathological evidence of pseudomembranous colitis; **and**
   C. The patient does not have **any** of the following contraindications (1. - 5.):
      1. Patient is immunocompromised, including any of the following (a. – e.):

a. Patients on major immunosuppressive agents (e.g., high-dose corticosteroids, calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, lymphocyte-depleting biological agents, anti-tumor necrosis factor agents, chemotherapeutic antineoplastic agents)
b. Advanced HIV/acquired immune deficiency syndrome
c. Recent bone marrow transplant
d. Decompensated liver cirrhosis
e. Other causes of severe immunodeficiency

2. Anatomic contraindications to nasogastric tube, enema, or colonoscopy (dependant on route of administration)
3. Pregnancy
4. Use of ongoing antibiotics for indications other than CDI
5. Toxic megacolon or ileus

II. Fecal microbiota transplantation is considered **investigational and not covered** when criterion I. above is not met, including but not limited to treatment for **any** of the following (A. - C.):

A. Initial episode or first recurrence/occurrence of CDI
B. When one of the contraindications noted above is present
C. For conditions other than CDI, including but not limited to, any of the following (1. - 11.):
1. Chronic fatigue syndrome
2. Constipation
3. Graft-versus-host disease of the gut
4. Hepatic encephalopathy
5. Inflammatory bowel disease (including ulcerative colitis Crohn's disease)
6. Intestinal multidrug-resistant bacterial decolonization
7. Irritable Bowel Syndrome
8. Metabolic syndrome
9. Obesity
10. Parkinson's disease
11. Pouchitis

Link to Policy Summary

BILLING GUIDELINES

- Fecal microbiota transplantation pills should be billed with HCPCS code J7999.
- Colonoscopy (or other instillation methods) may not be billed separately, as HCPCS code G0455 includes "instillation by any method."
- Use of codes other than HCPCS code G0455 for this procedure (e.g., 44705 or 44799) is not appropriate.

CPT/HCPCS CODES

All Lines of Business	
Prior Authorization Required	
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen
Not Covered	
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be **denied as not covered.**	
44799	Unlisted procedure, small intestine

DESCRIPTION

Fecal microbiota transplantation (FMT), also known as fecal bacteriotherapy, involves using one of several methods to introduce fecal matter from a healthy donor into the gastrointestinal tract of a patient with recurrent Clostridioides difficile (formerly known as clostridium difficile) (C. diff) infection (CDI) to recolonize the patient's colon with nonpathogenic bacteria.

Alternatives to FMT include surgical treatment (eg, colectomy), conventional antibiotic agents (metronidazole and vancomycin), alternative antibiotics (e.g., rifaximin, Fidaxomicin, fusidic acid), pulsed dosing of vancomycin, probiotics, and intravenous immunoglobulin against C. diff toxin.

FMT is administered by a gastroenterologist via nasogastric tube, nasoduodenal/jejunal tube, an upper-tract endoscope, a colonoscope, retention enema, or a combination of upper and lower methods. Recently, oral capsulized FMT has been introduced, which involves ingestion of several prepared capsules under direct supervision. At this time, no consensus exists on the preferred administration route, and no clear superiority of one method over another has been demonstrated.[1]

Alleged benefits of FMT include lower cost than several courses of antibiotics and hospitalization, rapid treatment and resolution compared to several weeks of antibiotics, mild to no side effects, and reduced risk of antibiotic-associated bacterial resistance.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of fecal microbiota transplantation (FMT) as a treatment for any indication. Below is a summary of the available evidence identified through April 2021.

Clostridioides difficile Infections (CDI)

Recurrent CDI (rCDI)

In 2020, ECRI updated a clinical evidence assessment of fecal microbiota transplantation for treating recurrent C. difficile infection.[2] The authors concluded that the evidence is somewhat favorable based on 1 systematic review with meta-analysis that included 8 randomized controlled trials and 1 additional RCT. Although sample studies were small in the RCTs included in the SR, overall quality of the studies was high and FMT was found to reduce diarrhea recurrence in patients with recurrent refractory CDI.

In 2016 (updated 2018; archived 2019), Hayes published a review of FMT for refractory or recurrent CDI, including four randomized controlled trials (RCTs) and eight retrospective series on adult populations.[3] Because studies including pediatric patients were limited, they were not included in the review. Overall, the review indicated that a small but moderate-quality body of evidence consistently reported that the use of FMT cures a large proportion of patients with refractory or recurrent CDI who had failed standard antibiotic treatment. The review stated that adverse events associated with FMT were generally rare and self-limiting. Two fair quality, moderately sized (n=39 and 43 adult patients) both reported a large magnitude of benefit among those receiving FMT compared with controls. In both RCTs, between 65-94% of patient who underwent FMT were cured after 10 weeks, compared to 23-26% of patients in control groups (p.0.01-0.0001). As a result, Hayes assigned a **rating of "B"** for use of FMT in adult patients with relapse of CDI after ≥ 1 courses of ≥ 10 days of oral vancomycin at 125 milligrams (mg) 4 times daily or > 10 days of oral metronidazole at 500 mg 3 times daily.

Similar conclusions were drawn by the 2017 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review, the Washington State Health Care Authority technology assessment on FMT, both of which included three of the same RCTs as the Hayes review above.[4,5]

Additional systematic reviews published after the ECRI and Hayes reviews reported similar conclusions regarding the use of FMT as a treatment for recurrent/refractory CDI.[6-11] Overall, systematic reviews on this therapy are in agreement that FMT is an effective treatment for recurrent and refractory CDI, with a relatively low rate of serious adverse events. One recent meta-analyses reported that the clinical effect varies with the delivery method and the number of administrations, suggesting that lower gastrointestinal endoscopy may be superior to all other delivery methods, and repeat FMT significantly increases the treatment effect.[12]

In a ten-year follow-up of patients treated with FMT for rCDI in a randomized controlled trial, Ooijevaar et. al reported that none of the patients had experienced a new-onset autoimmune, gastrointestinal, or malignant disorder during follow-up.[13] Of the 34 originally enrolled patients, 7 were still living and 3 were lost to follow-up at ten-years. No deaths were found to be attributable to FMT.

Initial CDI

The evidence for the use of FMT for treatment of an initial CDI is limited mainly to case reports and small case series, since the majority of studies have evaluated its use in the setting of recurrent infection. These studies have been small (n<7) and have reported mixed results.[14]

One small RCT was published that evaluated the use of FMT (donor-unrelated donor mix) to standard CDI treatment, though enrollment included participants with both initial and recurrent CDI.[15] The trial included 19 adult patients (16 available for analysis) that evaluated FMT as a first-line treatment compared to oral vancomycin. Symptoms resolved in 8/9 patients (88.9%) in the vancomycin group, while symptoms resolved in 4/7 patients (57.1%) after the first course of FMT and in 5/7 patients (71.4%) after the second course. Cure rates were not significantly different between treatment arms and patients treated with FMT did not have higher cure rates than those treated with conventional vancomycin therapy in this setting.

Other Indications

Inflammatory Bowel Disease (IBD) (Ulcerative colitis [UC] and Crohn's disease [CD])

- In 2014, Colman and Rubin conducted a systematic review on the use of FMT as a primary therapy for IBD, including 18 studies (9 cohort studies, 8 case studies and 1 RCT).[16] In total, 122 patients were described [79 ulcerative colitis (UC]; 39 Crohn's disease (CD); 4 IBD unclassified). Overall, 45% (54/119) of patients achieved clinical remission. Pooled estimates of clinical remission were 22% (95% CI 10.4%-40.8%) for UC and 60.5% (95% CI 28.4%-85.6%) for CD. Of note, there was significant heterogeneity (I^2 = 37%) between the cohort studies. The review concluded that there was variability between studies regarding FMT efficacy and that more RCTs are needed.

- One 2015 systematic review by Rossen et al., included seven case series (n= 6 cases of CD and 106 cases of UC) and reported clinical remission rates of 0-68% (n=3 case series) and clinical improvement rates between 20% and 92% (n=6 case series).[17] All seven studies were deemed of poor quality: small case series that were heterogenous in terms of site of IBD, measures of therapeutic response, clinical evaluation tools used, and inclusion of patients with CD. As a result, the review concluded that although FMT shows promise for IBD, additional studies are needed.

- In 2016, the Washington State Health Care Authority technology assessment on FMT, described above, evaluated its use as a treatment for IBD, including studies on ulcerative colitis (UC) and Crohn's disease(CD) .[5] The assessment only included two RCTs, and neither found any significant differences concerning clinical response or remission rates for FMT compared to placebo. Both studies had significant limitations. One study did not blind the patients, was small in size (n=38), and did not report confidence intervals. The larger RCT (n=75) was deemed to have a high risk of bias and had short-term follow-up (1.75 months). Overall, the technology assessment stated that there was sufficient evidence to evaluate the use of FMT for IBD, but that the studies suffered from methodological limitations and the quality of evidence was poor.

- Recent systematic reviews focused on the use of FMT for IBD and/or UC treatment have reported clinical remission rates between 28% and 40.5% in pooled analyses.[18-23] These reviews all contain the same methodological limitation including mainly case series that have small patient cohorts and lack a comparator group. Some reviews have also included case reports and conference abstracts. In addition, both sub-group and/or pooled analyses have been reported in these reviews to have modest but significant between-study heterogeneity. All reviews have

indicated that additional, better-designed RCTs are still required to confirm efficacy in this population.

No additional comparative studies, including RCTS, were identified that evaluated FMT as a treatment for IBD and/or UC since the most recent systematic reviews included above.

Other Conditions

In the 2015 systematic review by Rosset al. described above, studies were included which evaluated the use of FMT to treat constipation, pouchitis and irritable bowel syndrome (IBS). However, only one small case series was identified and evaluated for each of these conditions, and it were all determined to be of poor quality. The review also included one small RCT (n=18 male patients) which reported on the use of FMT for metabolic syndrome, evaluating patients six -weeks post FMT. The review concluded that there was insufficient evidence to draw conclusions about the efficacy of FMT as a treatment for any of these conditions.

Only two RCTs were identified after the publication of the Rossen et al. systematic review on conditions other than CDI and IBD, which are described below. However, these are the first RCTs to evaluate the use of FMT for these conditions, and additional larger RCTs with longer term follow-up are needed.

In 2017, Tian et al. published a small RCT on the use of FMT to treat constipation, including patients randomly assigned to conventional treatment alone (n = 30) or FMT (n = 30) through a nasointestinal tube. [24] The authors reported modestly significant differences between the intervention group and control group in the clinical cure rate (36.7% vs. 13.3%, p = 0.04), and additional outcome measures. However, the FMT group had more treatment-related adverse events than did the control group (50 vs. 4 cases) and the study had limited follow-up (12 weeks).

In 2018, Bajaj et al. published a small RCT (n=20 patients, 10 per treatment group) evaluating FMT for treatment of hepatic encephalopathy compared to standard of care.[25] The authors only reported adverse events, not patient-specific health outcomes such as cure rate, and noted that treatment with placebo antibiotics, sham FMT or autologous FMT, may have been more appropriate for the control arm. This RCT was limited by the fact that the FMT treatment group was also treated with pretreatment antibiotics, making it difficult to discern the precise role of FMT alone. Given the given the selected donor approach used in this study, the results may not be generalized to FMT from different donors and administration routes.

FMT has also been evaluated in small case series and case reports as a potential treatment for chronic fatigue syndrome,[26] graft-versus-host disease of the gut,[27,28] intestinal multidrug-resistant bacterial decolonization,[29] irritable bowel syndrome,[30] hepatic encephalopathy,[31] and Parkinson's disease.[32] Due to the small number of patients evaluated for these conditions, conclusions cannot be drawn regarding the efficacy of FMT for these conditions.

CLINICAL PRACTICE GUIDELINES

Infectious Diseases Society of America (IDSA)/ Society for Healthcare Epidemiology of America (SHEA)

In 2018, the IDSA/SHEA published joint clinical practice guidelines for clostridium difficile infection in adults and children.[33] This was an update to the previous 2010 guidelines and was completed in 2017. This high quality guideline was informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options, including literature published up to the end of 2016.

***Initial Occurrence of CDI*:**

> "Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of CDI." This was a strong recommendation based on high quality evidence and was recommended regardless of disease severity.
>
> "In settings where access to vancomycin or fidaxomicin is limited, we suggest using metronidazole for an initial episode of nonsevere CDI only." This was a strong recommendation based on moderate quality evidence.
>
> For fulminant CDI, previously referred to as sever, complicated CDI, "vancomycin administered orally is the regimen of choice (strong recommendation, moderate quality of evidence). If ileus is present, vancomycin can also be administered per rectum (weak recommendation, low quality of evidence)."

Recurrent or Recalcitrant CDI:

> First recurrence: Treatments included either vancomycin or fidaxomicin, depending on antibiotic used during the first occurrence. These were weak recommendations, based on moderate to low quality evidence.
>
> Second or subsequent recurrence: FMT was listed as an option for recurrent CDI, with the guideline stating "[FMT] is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments." This was a strong recommendation, but is only to be considered after the second recurrence. The guideline stated, "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." This same recommendation was extended to children, but was a weak recommendation, based on low quality evidence.

American Society of Colon and Rectal Surgeons (ASCRS)

In 2015, the ASCRS published evidence-based practice parameters for the management of Clostridium difficile infection that recommended the following:[34]

***Initial Occurrence of CDI*:**

> "Both metronidazole and vancomycin are acceptable first-line agents for an initial bout of CDI, with selection normally based on disease severity." This was a strong recommendation based on moderate-quality evidence (RCTs with limitations).
>
> "Surgery [] should typically be reserved for patients with severe colitis that fails to improve with medical therapy, for generalized peritonitis, or for rare cases of colonic perforation." This was a strong recommendation, but was based on low-quality evidence (observational studies or case series with limited long term follow-up).

Recurrent or Recalcitrant CDI:

> First line treatments for recurrent CDI (defined as recurrent diarrhea AND a positive fecal sample for C diff. or its toxins, or colonoscopic/histopathologic evidence of pseudomembranous colitis) include either metronidazole or vancomycin. This was a strong recommendation, but was based on low quality evidence.
>
> FMT was listed as one of several alternative treatments, with the guideline stating: "Patients with refractory CDI may be considered for fecal bacteriotherapy (intestinal microbiota transplantation) if conventional measures have failed." This was a strong recommendation based on low quality evidence. However, the guideline indicated that "it is recommended that conventional methods of treatment should be sequentially exhausted before considering fecal bacteriotherapy".
>
> The guideline also noted that, "best practices for this treatment modality still need to be developed with regard to patient selection, donor selection, and fecal transplant protocol as further experience with this technique evolves."

National Institute for Health and Care Excellence (NICE)

In 2014, NICE issued an interventional procedure guidance for fecal microbiota transplant (FMT) for the treatment of recurrent CDI, stating the following:[35]

> "Current evidence on the efficacy and safety of [FMT] for recurrent C. difficile infection is adequate to support the use of this procedure…. The procedure should only be considered for people with recurrent C. difficile infections that have failed to respond to antibiotics and other treatments."

The guidance stated that first line treatment includes rehydration and antibiotic therapy, but did not expand further.

American College of Gastroenterology (ACG)

In 2013, the ACG published evidence-based practice guidelines for the diagnosis, treatment and prevention of Clostridium difficile infection.[36]

***Initial Occurrence of CDI*:**

Either metronidazole or vancomycin were recommended as first-line agents, depending disease severity and intolerance/allergies. These were typically strong recommendations based on high- to moderate-quality evidence. Severe CDI treatment recommendations included modified vancomycin protocols (strong recommendation based on low quality evidence) and surgery in select patients (strong recommendation based on moderate quality evidence).

Recurrent or Recalcitrant CDI:

First-line treatment for recurrent CDI, defined as recurrence within 8 weeks of completion of therapy, is metronidazole or pulsed vancomycin regimen. The ACG cautioned against the use of fidaxomicin due to insufficient evidence of superiority over vancomycin.

Fecal transplant should be considered, "if there is a third recurrence following a pulsed vancomycin regimen". This was a conditional (moderate strength) recommendation (uncertainty exists about the risk-benefit ratio) based on moderate-quality evidence.
The ACG noted that long-term follow-up for any treatment of recurrent CDI is limited and the potential for transmission of infectious agents is a concern.

CENTERS FOR MEDICARE & MEDICAID

As of 04/03/2021, no Centers for Medicare & Medicaid (CMS) coverage guidance was identified which addresses fecal microbiota transplantation for any indication.

POLICY SUMMARY

Fecal Microbiota Transplantation for Recurrent Clostridium Difficile Infections

There is sufficient evidence to show that the use of fecal microbiota transplantation (FMT) may improve overall health outcomes for those with recurrent Clostridium difficile infections (CDI), when previous occurrences have not been helped antibiotics. In addition, clinical practice guidelines support the use of FMT in select patients. Therefore, the use of FMT for the treatment of CDI may be considered medically necessary and covered when policy criteria are met.

Fecal Microbiota Transplantation for Initial Clostridium Difficile Infections

There is not enough research to show that use of fecal microbiota transplantation (FMT) as a treatment for an initial occurrence of Clostridium difficile infections (CDI) improves cure rates when compared with antibiotic treatment. The existing research is nonrandomized and/or of low quality. In addition, no clinical practice guidelines based on research recommend FMT for first-time CDI. Therefore, the use of fecal microbiota transplantation for initial occurrence of Clostridium difficile infection is considered investigational and not covered.

Fecal Microbiota Transplantation for Other Investigational Indications

Inflammatory Bowel Disease

There is not enough research to show that fecal microbiota transplantation (FMT) used as a treatment for inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, improves overall health outcomes when compared with other treatments or placebo. The existing research is of nonrandomized and/or of low quality. Only two randomized controlled trials were identified, and neither found any significant clinical response or remission rates differences between FMT treatment compared to placebo. Systematic reviews of the use of FMT for IBD report that conclusions regarding the efficacy of FMT in this setting cannot be drawn at this time. No clinical practice guidelines were identified that address FMT as a treatment option for inflammatory bowel disease, Crohn's disease or ulcerative colitis. Therefore fecal microbiota transplantation for the treatment of inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is considered investigational and not covered.

Other Indications

There is not enough research to that fecal microbiota transplantation (FMT) used as a treatment for other conditions not addressed above, including but not limited to constipation and metabolic syndrome, improves overall health outcomes when compared with other treatments or placebo. No clinical practice guidelines were identified that address FMT as a treatment option for any indication other than Clostridium difficile infections. Therefore, FMT used as a treatment for other conditions not addressed above, is considered investigational and not covered.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

U.S. Food and Drug Administration (FDA) Regulation of Fecal Microbiota for Transplantation

Currently, the FDA has classified human stool as a biological agent and determined that its use in fecal microbiota transplantation (FMT) therapy and other research should be regulated to ensure patient safety. To use FMT to treat recurrent Clostridium difficile infection (CDI), an investigational new drug

(IND) permit is not required, but is strongly encouraged. Therefore, the use of FMT for recurrent CDI does not require FDA-approval.

However, the use FMT for research or to treat any condition other than recurrent CDI, required an IND permit approved by the FDA.

Per the FDA **Draft** Guidance for Industry on FMT for refractory CDI (published in March 2016):[37]

> "FMT administered to treat *C. difficile* infection meets the definition of a biological product, as defined in section 351(i) of the PHS Act (42 U.S.C. 262(i)), in that it is a regulated article applicable to the prevention, treatment, or cure of a disease or condition of human beings. It also meets the definition of a drug within the meaning of section 201(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)), in that it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or is intended to affect the structure or any function of the body of man. As a biological product, FMT administered to treat *C. difficile* infection is subject to the licensing requirements set forth in section 351 of the PHS Act (42 U.S.C. 262). It is, however, exempt from these licensing requirements when administered pursuant to an IND application and in compliance with the IND regulations set forth in 21 CFR Part 312. (See 42 U.S.C. 262(a)(3))."

This guidance is in draft form only, is still open for comments and has not been approved by the FDA in its final form.

In June 2019, the FDA advised that stool donors for fecal microbiota transplantation be screened with questions that specifically address risk factors for colonization with Multi Drug Resistant Organisms (MDROs), and individuals at higher risk of colonization with MDROs should be excluded as donors.[38] In addition, FDA scientists advised that donor stool should be specifically tested for MDROs and not used if positive.

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

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