



# Louisiana

## Fecal Microbiota Transplantation

**Policy #** 00441

**Original Effective Date:** 08/20/2014

**Current Effective Date:** 11/01/2018

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **When Services May Be Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider fecal microbiota transplantation (FMT) for treatment of patients with recurrent *Clostridium difficile* infection (CDI) to be **eligible for coverage** (See Policy Guidelines section).

### Patient Selection Criteria

Coverage eligibility may be considered for FMT for treatment of patients with recurrent CDI when all of the following criteria are met:

- There have been at least 3 episodes of recurrent infection; and
- Episodes are refractory to appropriate antibiotic regimens, including at least 1 regimen of pulsed vancomycin.

### **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers FMT in all other situations to be **investigational**.\*

The use of FMT for treatment of patients with recurrent CDI when patient selection criteria are not met is considered to be **investigational**.\*

### **Policy Guidelines**

There is a lack of consensus on the number of recurrences that warrants consideration of FMT.

Among the 2 published randomized controlled trials (RCTs) evaluating FMT for treatment of CDI, the van Nood study (2013) included patients with at least 1 recurrence of CDI; the other study, the Youngster study (2014), included patients with a relapse after at least 3 episodes of mild-to-moderate CDI or at least 2 episodes of severe CDI (both studies are described in the Rationale section.)

The 2013 American College of Gastroenterology guidelines recommended that FMT be considered second-line therapy for a third recurrence of CDI.

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### **Background/Overview**

#### **FECAL MICROBIOTA**

FMT, also called donor feces infusion, intestinal microbiota transplantation, and fecal bacteriotherapy, involves the infusion of intestinal microorganisms via 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 the stool can be infused 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 10 times the number of human cells. Most human microbes reside in the intestinal tract, and most of these are bacteria. In its healthy state, intestinal microbiota perform a variety of useful functions including aiding in the digestion of carbohydrates, mediating the synthesis of certain vitamins, repressing the growth of pathogenic microbes, and stimulating the lymphoid tissue to produce antibodies to pathogens.

### **Applications**

#### ***Clostridium difficile* Infection**

To date, the major potential clinical application of FMT is the treatment of 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 intestinal flora. The incidence of CDI in North America has increased substantially in the past decade. For example, according to hospital discharge diagnosis data, there were more than 300,000 cases of CDI in 2006 compared with fewer than 150,000 cases in 2000. Moreover, CDI causes an estimated 15,000 to 20,000 deaths per year in U.S. hospitals.

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 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 FMT include treatment of conditions in which altered colonic flora may play a role. They include inflammatory bowel disease (IBD), irritable bowel syndrome, idiopathic constipation, and non-gastrointestinal disease 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.

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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, published in 2013, evaluated a synthetic stool product in 2 patients with recurrent CDI. The product is made from 33 bacterial isolates developed from culturing stool from a healthy donor.

### **FDA or Other Governmental Regulatory Approval**

#### **U.S. Food and Drug Administration (FDA)**

In July 2013, the U.S. FDA issued guidance on investigational new drug requirements for the use of FMT to treat CDI not responsive to medication therapy. The FDA guidance stated that FDA 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 infections. FDA 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 use of fecal transplant for treating conditions other than treatment-resistant CDI.

#### **Centers for Medicare and Medicaid Services (CMS)**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### **Rationale/Source**

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a RCT that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition. The following is a description of the key literature to date.

### **RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION**

The available literature on CDI consists of RCTs, numerous uncontrolled studies, and systematic reviews. Other than a few case reports of patients with acute CDI, studies treated patients with recurrent infection.

#### **Systematic Reviews**

In 2015, Drekonja et al systematically reviewed the literature on FMT for treating CDI. In addition to the 2 RCTs, reviewers identified 28 case series and 5 case reports. Twenty-one case series included patients with recurrent CDI in these studies, 85% of patients treated with FMT remained free of symptoms without additional recurrences (the number of patients successfully treated was not reported). Seven case series included patients with refractory CDI, defined as an episode of CDI that did not respond to antimicrobial treatment. Resolution of symptoms in the studies on refractory CDI ranged widely, from 0% to 100%, with

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an overall resolution rate of 55%. There were reports of only 7 patients treated with FMT for initial CDI. The case series reported few adverse events.

In 2017, Quraishi et al published a systematic review and meta-analysis of 7 RCTs comparing FMT with standard antibiotic regimen in 1973 patients with recurrent and refractory CDI (follow-up, 10-13 weeks), and 30 case series (sample sizes  $\geq 10$  patients) describing the effect of FMT in 1545 patients with recurrent and refractory CDI. Reviewers deemed the 7 RCTs as having a low risk of bias (including adequate randomization with allocation concealment and intention-to-treat analysis). Reviewers did not report an assessment of bias in terms of blinding, sample size adequacy, or possible differences in baseline characteristics. They argued that none of trials examining the efficacy of FMT were truly placebo controlled, and the 30 case series followed patients until resolution of CDI (range, 10 weeks to 8 years), though some had incomplete follow-up. In the pooled analysis, 92% of patients had a resolution of CDI (95% confidence interval [CI], 89% to 94%); heterogeneity were classified as likely moderate ( $I^2=59\%$ ). Additionally, in the 7 trials that evaluated FMT, the intervention overall was associated with an increase in the resolution of recurrent and refractory CDI (relative risk [RR], 0.23; 95% CI, 0.07 to 0.80). The 30 case series reported resolution rates for CDI from 68% to 100%.

The Quraishi review found FMT to be effective in the treatment of recurrent and refractory CDI, and no serious adverse events from FMT were reported in the RCTs through the follow-up period. Most adverse effects in the case series were minor (bloating, belching, abdominal cramps, pain or discomfort, nausea, vomiting, excess flatulence, constipation, transient fever, urinary tract infections, self-limiting diarrhea, irregular bowel movement). However, reviewers noted several limitations. Based on variability in the definitions of CDI resolution used across the studies, reviewers could not distinguish between recurrent and refractory CDI. There were also variations across studies in terms of recipient preparations, number of infusions, time to resolution, follow-up, overall response, dosing, concurrent use of medications, and other nonspecified biases. Heterogeneity between most studies was considerable.

### Randomized Controlled Trials

In 2013 van Nood et al published a nonblinded trial that included 43 patients 18 years and older with at least 1 recurrence of CDI. Exclusion criteria included prolonged compromised immunity, admission to an intensive care unit, and need for vasopressor medication. Patients were randomized to 1 of 3 treatment groups: (1) FMT (here called donor feces infusion;  $n=17$ ); (2) antibiotic therapy ( $n=13$ ); or (3) antibiotics and bowel lavage ( $n=13$ ). The FMT intervention involved collecting feces from healthy screened donors on the day of infusion, diluting the feces with 500 mL of sterile saline, and infusing the solution (mean, 141 g) through a nasoduodenal tube. Patients assigned to the FMT group also received a modified course of vancomycin (500 mg orally 4 times a day for 4-5 days) and bowel lavage before infusion. A second infusion was given to patients in the FMT group who relapsed after the first treatment. Potential donors underwent an evaluation that included completing a questionnaire on potential risk factors for transmissible diseases, screening feces for parasites, and blood screening for antibodies for viruses. The trial was initially designed to enroll 120 patients (40 per group), but, because of the high relapse rate in the control groups, the data and safety monitoring group recommended early trial termination.

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The primary efficacy outcome was cure without relapse within 10 weeks of initiating treatment. Cure was defined as absence of diarrhea that could not be explained by other causes and 3 consecutive negative tests for CDI toxin. Relapse was defined as diarrhea with a positive stool test for CDI toxin during this 10-week period. For the 3 patients who received a second infusion, follow-up was extended to 10 weeks after the second treatment. Patients were questioned about symptoms of diarrhea, and stool tests were performed on days 14, 21, 35, and 70 and when diarrhea was reported. One patient in the FMT group was excluded from analysis.

Fifteen (94%) of 16 analyzed patients in the FMT group were cured (13 after a single infusion, 2 after a second infusion from a different donor). In contrast, only 4 (31%) of 13 patients in the antibiotics-only group and 3 (23%) of 13 patients in the antibiotics and bowel lavage group were cured. The overall cure rate was significantly higher in the FMT group than in the other 2 groups ( $p < 0.001$ ). Most patients in the FMT group experienced short-term adverse events (i.e., diarrhea in 94%, cramping in 31%, belching in 19%) that resolved within 3 hours.

Data on the diversity of fecal microbiota were available for 9 patients in the FMT group. Diversity was measured on a scale from 1 to 250, with higher values indicating more diversity. Before infusion, mean microbiota diversity was low (mean, 57, SD=26). Within 2 weeks of infusion, mean diversity increased to 179 (SD=42), a level similar to the diversity levels in the donors (mean, 172; SD=54).

Kelly et al (2016) published the findings from a multicenter, double-blinded RCT that included 46 patients (mean age, 48-55 years) who had 3 or more recurrences of CDI and received a full course of vancomycin for their most recent acute episode. Patients were randomized to FMT with donor stool (heterologous, n=22) or patient's personal stool (autologous, n=24) administered by colonoscopy. There were possible baseline differences in the mean duration of CDI since initial dose, mean CDI recurrences, and the prior use of *Lactobacillus*, fidaxomicin, or proton-pump inhibitor. Forty-three patients completed the 8-week follow-up evaluation, and the principal investigators terminated enrollment after 28 months in light of data on the efficacy of FMT. However, the intention-to-treat analysis included all enrolled patients.

Both patients and screened donors provided fresh stool the day of the FMT and randomization occurred shortly before the procedure. By protocol, stool 100 g was diluted in 500 mL 0.9% normal saline (or a proportional amount of saline if less stool was available). The physician administered 300 mL of fecal suspension via colonoscopy.

The primary end point was CDI resolution, defined as the resolution of diarrhea without the need for further anti-CDI therapy throughout the follow-up period. Fecal microbiota analyses of patient and donor stool before and after FMT demonstrated an overall CDI resolution of 90.9% in the heterologous FMT group compared with a CDI resolution of 62.5% in the autologous FMT group ( $p = 0.042$ ). However, there were notable differences in efficacy by site. CDI resolution with heterologous FMT at the first site was 90.0% (95% CI, 51.8% to 98.7%) vs 42.9% (95% CI, 20.1% to 69.0%) with autologous FMT. The second site reported CDI resolution with heterologous FMT to be 91.7% (95% CI, 57.2% to 98.9%) compared with 90.0% (95% CI, 51.8% to 98.7%) in the autologous FMT group. The authors cautioned that the observed

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variability in efficacy between sites suggested that patients who have a lower risk of CDI recurrence may not benefit from FMT. For patients with clinical failure, failure occurred at a mean of 10 days postprocedure. Rates of adverse events were similar in the 2 groups. Four serious adverse events were reported, but none of the events were attributed to FMT or colonoscopy. Reported study limitations included the following factors:

- no data collection on the severity of previous CDI episodes or antibody titers;
- possibly limited representation of the CDI population due to the exclusion of patients aged 75 or older;
- possibly limited representation of the CDI population due to the inclusion of a younger cohort of patients;
- dosing differences;
- the possibility of overdiagnosis of CDI due to the use of polymerase chain reaction testing of stool to diagnose CDI;
- and the lack of power to assess rare, severe adverse events.

### **Uncontrolled Studies**

Several systematic reviews of uncontrolled studies on FMT for treating CDI have been published. Of these, only Sofi et al (2013) conducted a pooled data analysis. Reviewers searched the literature through April 2012, and could not find any RCTs that evaluated FMT (none had been published at that time). Reviewers did find a total of 25 observational studies (10 case reports, 15 case series), which provided data on 239 adults treated with FMT for CDI. All case series were retrospective, and sample sizes ranged from 4 to 70 patients; only 4 studies included more than 25 patients. Most studies included recurrent CDI, but several case reports treated patients who were severely ill due to acute CDI. Fecal transplants were performed by the gastroduodenal route in 91 (32%) patients and by the colonic route in 198 (68%) patients. Treatment success was defined as resolution of CDI symptoms at follow-up. Mean follow-up posttransplant ranged from 10 days to 65 months. In a pooled analysis of individual patient data, the overall treatment success rate was 91.2%. Subgroup analyses revealed a significantly higher treatment failure rate in patients treated colonically vs the duodenal route; moreover, these analyses revealed a higher treatment failure rate in patients who experienced symptoms for at least 60 days vs fewer than 60 days.

### **Procedural Approaches**

#### ***Route of Administration***

##### *Systematic Reviews*

The 2017 systematic review and meta-analysis by Quraishi et al (discussed previously) included a subgroup analysis of FMT delivery. Pooled analysis of 7 RCTs and 25 case series revealed a significant difference between lower gastrointestinal delivery (95%; 95% CI, 92% to 97%) and upper gastrointestinal delivery (88%; 95% CI, 82% to 94%;  $p=0.02$ ). Reviewers concluded that FMT appeared to be effective in the treatment of recurrent and refractory CDI, independent of delivery route.

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### *Randomized Controlled Trials*

A 2014 RCT by Youngster et al compared infusion of donor stools administered by colonoscopy or nasogastric tube. Twenty patients with relapsing and recurrent CDI were included. Patients had to have a relapse of CDI following at least 3 episodes of mild-to-moderate CDI and failure of a course of vancomycin, or at least 2 episodes of severe CDI that resulted in hospitalization and was associated with significant morbidity. All patients underwent FMT and were randomized to 1 of 2 infusion routes: colonoscopy or nasogastric tube. Both groups received thawed inoculum 90 mL. Stool donors were healthy nonrelatives who successfully completed an extensive screening process. Stool was frozen up to 156 days before use. Patients could receive a second FMT if symptoms did not resolve following the initial transplant. The primary efficacy outcome was clinical cure, defined as resolution of diarrhea (i.e., <3 bowel movements per 24 hours) while off antibiotics for CDI, without relapse for 8 weeks. Fourteen patients were cured after the first FMT, eight in the colonoscopy group and six in the nasogastric tube group; the difference between groups was not statistically significant ( $p=0.628$ ). Of the remaining 6 patients, one refused additional treatment, and the other five underwent a second transplant. By study protocol, patients could choose the route of administration for the second procedure, and all chose the nasogastric tube. Four additional patients were cured after the second transplant, for an overall cure rate of 18 (90%) of 20. This trial did not find either route of administration of donor feces to be superior to the other; however, it was reported that patients preferred nasogastric tube.

### **Fresh vs Frozen Feces**

#### *Systematic Reviews*

The 2017 Quraishi systematic review also included a subgroup analysis of FMT preparation. Only 1 RCT in the review directly compared the effects of fresh stool to prepare FMT ( $n=11$ ) with frozen stool to prepare FMT ( $n=108$ ) on CDI resolution (RR=1.19; 95% CI, 0.77 to 1.84). The remaining 30 case series used frozen stool to prepare FMT. Two RCTs and 2 case series used fresh stool to prepare FMT. The pooled analyses found no difference between fresh FMT (92%; 95% CI, 89% to 95%), with moderate heterogeneity ( $I^2=54%$ ) and frozen FMT (93%; 95% CI, 87% to 97%;  $p=0.84$ ), with minimal heterogeneity reported ( $I^2=19%$ ). Reviewers concluded that FMT appeared to be effective in the treatment of recurrent and refractory CDI, independent of FMT preparation.

#### *Randomized Controlled Trials*

A 2016 double-blind RCT by Lee et al compared fresh with frozen stool used in FMT to treat patients with recurrent CDI. A total of 232 patients were included, 114 assigned to frozen FMT and 118 to fresh FMT. The primary end point was the proportion of patients with no recurrence of CDI-related diarrhea 13 weeks after FMT. The trial was designed as a noninferiority trial and had a noninferiority margin of 15%. In the per-protocol population ( $n=178$ ), the rate of clinical resolution of symptoms was 76 (83.5%) of 91 in the frozen FMT group and 74 (85.1%) of 87 in the fresh FMT group (difference, -1.6%; 95% 1-sided CI, -10.5% to infinity). In the modified intention-to-treat group, the rate of clinical resolution with up to 2 FMT treatments was 81 (75.0%) of 108 in the frozen FMT group and 78 (70.3%) of 111 in the fresh FMT group (difference, 4.7%; 95% 1-sided CI, -5.2% to infinity). The difference between groups was within the 15% noninferiority margin, and thus frozen FMT was considered noninferior to fresh FMT.

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### **Section Summary: Recurrent *Clostridium difficile* Infection**

A systematic review and meta-analysis of 7 RCTs and 30 case series concluded that FMT appeared to be effective in the treatment of recurrent and refractory CDI, independent of preparation and route of delivery. One small RCT, which enrolled patients who had failed at least 1 course of antibiotic treatment, reported a large increase in resolution of CDI with FMT plus antibiotics compared with antibiotics with or without bowel lavage. A double-blinded, multicenter RCT using fresh heterologous stool administered via colonoscopy; patients in this RCT had 3 or more recurrences of CDI and received a full course of vancomycin. Moreover, reviewers found FMT to be effective in preventing further episodes of CDI during an 8-week follow-up period. RCTs evaluating procedural differences found similar success rates with FMT administered via colonoscopy vs gastric tube and with fresh vs frozen FMT. Uncontrolled studies have reported high rates of resolution of recurrent CDI following treatment with FMT.

## **INFLAMMATORY BOWEL DISEASE**

### **Randomized Controlled Trials**

In 2015, 2 double-blind placebo-controlled randomized trials evaluated FMT for treatment of ulcerative colitis (UC). Both trials were discontinued due to futility but one ultimately had positive findings. The 2 RCTs varied in their control conditions, outcomes measures, and intervention lengths.

Moayyedi et al (2015) enrolled 75 patients aged 18 and older with active UC (Mayo Clinic score  $\geq 4$ , endoscopic Mayo Clinic score,  $\geq 1$ ) and without CDI. Patients were randomized to FMT (n=38) or placebo (n=37). The intervention consisted of 6 weekly treatments with donor stool solution or placebo, given as a retention enema. Donors were screened prospectively for pathogens and rescreened every 6 months. Patients underwent clinical and endoscopic examination at week 7 ( $\pm 3$  days). The primary outcome was UC remission at week 7, defined as a full Mayo score less than 3 and a flexible sigmoidoscopy finding of complete healing of the mucosa (endoscopic Mayo score, 0).

The investigators initially aimed to recruit 130 patients. After 50% of participants were enrolled, the data monitoring and safety committee recommended trial discontinuation for futility, and completion of the trial for enrolled patients. At the 7-week follow-up, 9 (24%) of 38 patients in the FMT group and 2 (5%) of 37 patients in the placebo group achieved UC remission. The difference between groups was statistically significant ( $p=0.03$ ). There was no significant difference between groups in adverse event rates.

Rossen et al (2015) included 50 patients with mild to moderately active UC. To participate, patients had to have a patient-reported Simple Clinical Colitis Activity Index score between 4 and 11, an endoscopic Mayo score of 1 or more, and stable medication use. Patients were randomized to 2 treatments with FMT, 3 weeks apart, or a placebo intervention (autologous FMT). FMT was done via a nasoduodenal tube using fecal suspension 500 mL. Patients underwent clinical and endoscopic examination at baseline, 6 weeks, and 12 weeks. The primary end point was clinical remission at 12 weeks, defined as an Simple Clinical Colitis Activity Index score of 2 or less and at least a 1-point improvement on the combined Mayo endoscopic score of the sigmoid and rectum.

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Investigators initially calculated that a sample size of 42 patients was needed for the primary outcome analysis. The sample size calculated assumed a response rate of 70% in the treatment group and 22.5% in the control group. At the first interim analysis, after 20 patients had completed 12 weeks of follow-up, a lower response rate was observed and an increase in the sample size was recommended. At the second interim analysis, the data monitoring and safety committee recommended terminating the trial for futility. At study termination, 50 patients had been randomized. Two patients were excluded from the study postrandomization, leaving 48 patients in the intention-to-treat analysis. Thirty-seven patients completed the study. In the intention-to-treat analysis of the primary outcome measure, 7 (30.4%) of 23 patients in the active FMT group and 8 (32%) of 25 patients in the control group met criteria for clinical remission. The difference between groups was not statistically significant ( $p=1.0$ ). Four patients (2 in each group) experienced a serious adverse event. Other than 1 case of abdominal pain, the serious adverse events were not considered treatment-related. Most patients experienced mild adverse events during or shortly after treatment, the most common of which were transient borborygmus and increase in stool frequency.

### Uncontrolled Studies

In 2014, Sha et al published a systematic review of observational data on FMT for treatment of IBD. Reviewers identified reports of 111 IBD patients (UC and Crohn disease) worldwide who received fecal transplants for IBD. All studies were case series. Remission was achieved in 87 (77.8%) of 111 IBD patients.

### Section Summary: Inflammatory Bowel Disease

Two small RCTs on FMT for treatment of UC have been published. Both trials were discontinued for futility, and poor data (data were from already enrolled patients and were already analyzed). One trial found a statistically significant higher remission rate after active FMT than after a control intervention, but the implications of this finding are tempered by the low numbers of patients with remission ( $n=11$ ) and short follow-up (7 weeks). The other trial reported no difference in remission rates. This evidence is not sufficient to permit conclusions on the efficacy of FMT for UC. Additionally, questions remain about the optimal route of administration, donor characteristics, and number of transplants. Data on a small number of patients with Crohn disease are available, and there are no controlled studies of FMT in this population.

### POUCHITIS, IRRITABLE BOWEL SYNDROME, CONSTIPATION, OR METABOLIC SYNDROME

A 2015 systematic review by Rossen et al of studies on FMT identified 1 case series on constipation ( $N=3$  patients), 1 on pouchitis ( $N=8$  patients), and 1 on irritable bowel syndrome ( $N=13$  patients). There was also 1 small RCT ( $N=18$ ) on FMT for treatment of metabolic syndrome. The RCT by Vrieze et al (2012) compared donor microbiota transplantation with placebo (reinfusion of own collected feces). The authors found a significantly greater improvement in peripheral insulin sensitivity in the active FMT group but no difference between groups in hepatic insulin sensitivity.

### Section Summary: Pouchitis, Irritable Bowel Syndrome, Constipation, or Metabolic Syndrome

There is insufficient evidence on the efficacy and safety of FMT for treating conditions including pouchitis, irritable bowel syndrome, constipation, and metabolic syndrome. The evidence consists primarily of a few

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small case series; a small RCT on FMT for treating metabolic syndrome had mixed findings and did not report clinical outcomes (e.g., symptom improvement).

### **ADVERSE EVENTS**

In 2016, Wang et al published a systematic review of adverse events associated with FMT. Reviewers identified 50 publications (total N=1089 FMT-treated patients). Of these, 831 patients were affected by CDI, 235 had IBD, and the remainder had miscellaneous indications. The overall incidence of adverse events in the studies was 28.5% (310/1089). Most reported adverse events were mild-to-moderate in severity and included abdominal cramping, flatulence, fever, and belching. A total of 9.2% (100/1089) patients developed serious adverse events. Thirty-eight patients died. Reviewers attributed 1 death to be definitely related to FMT, 2 were possibly related, and 35 were unrelated. The definitely related death was due to aspiration during colonoscopy sedation, and the two possibly related deaths were associated with infections (due either to FMT or the patients' immunocompromised state). The incidence of severe infection was 2.5% (27/1089). Reviewers categorized 8 cases of severe infection as probably or possibly related to FMT; the other 19 cases were categorized as unrelated.

### **SUMMARY OF EVIDENCE**

For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT, the evidence includes RCTs and observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The RCTs found that FMT was more effective than standard treatment or placebo for patients with recurrent CDI. Other RCTs did not find the superiority of any route of administration over another or the superiority of fresh vs frozen feces. Case reports and case series have reported high rates of resolution of recurrent CDI following treatment with FMT. 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 IBD who receive FMT, the evidence includes 2 RCTs in patients with UC as well as observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Two small RCTs on FMT for treatment of UC were discontinued due to futility and poor data analyzed for patients already enrolled. Of the 2 small RCTs, one found a statistically significant higher remission rate after active FMT than after a control intervention, but this trial had few patients in remission (n=11) and short follow-up (7 weeks); the other trial reported no difference in remission rates. Data on a small number of patients with Crohn disease are available; however, there are no controlled studies of FMT in this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have pouchitis, irritable bowel syndrome, constipation, or metabolic syndrome who receive FMT, the evidence includes a small number of case series and/or case reports. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Data are available for only a limited number of patients, and there is a lack comparative studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

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# Louisiana

## Fecal Microbiota Transplantation

Policy # 00441

Original Effective Date: 08/20/2014

Current Effective Date: 11/01/2018

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### **Policy History**

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08/07/2014 Medical Policy Committee review

08/20/2014 Medical Policy Implementation Committee approval. New policy.

08/06/2015 Medical Policy Committee review

08/19/2015 Medical Policy Implementation Committee approval. No change in coverage.

08/04/2016 Medical Policy Committee review

08/17/2016 Medical Policy Implementation Committee approval. No change in coverage.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

08/03/2017 Medical Policy Committee review

08/23/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

08/09/2018 Medical Policy Committee review

08/15/2018 Medical Policy Implementation Committee approval. Changed the number of recurrent infection episodes from "2" to "3" in the first bullet of the Patient Selection Criteria. Added a Policy Guidelines section.

Next Scheduled Review Date: 08/2019

### **Coding**

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	44705
HCPCS	G0455
ICD-10 Diagnosis	A04.7

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\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

\*\*Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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