**Clinical Review Criteria**

**Fecal GI Infusion for the Treatment of C. Difficile Infection**

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<td>“Fecal GI Infusion for the Treatment of C. Difficile Infection” for medical necessity determinations.</td>
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For Non-Medicare Members

Fecal GI infusion is covered when **ALL of the following** are met:

1) Clostridium difficile infection confirmed by a positive stool test for C. difficile toxin
2) Has had at least two recurrences following adequate antibiotic therapy This would be defined as a symptomatic toxin-positive failure after at least one prolonged tapering course of vancomycin (generally over a 4-6 week period).

**FMT capsule, G3 OpenBiome**

If the above criteria are met, oral, capsulized, frozen fecal microbiota transplantation (FMT capsule, G3 OpenBiome) for the treatment of recurrent or refractory clostridium difficile infection is covered.

The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

**Background**

Clostridium difficile (C difficile) is the leading cause of antibiotic associated diarrhea and its rates continue to rise. During the past several years, the incidence of C difficile infection (CDI) has increased to an epidemic level; it has become more severe, more refractory to standard treatment, and more likely to relapse. According to the CDC, the number of hospitalized patients with any CDI discharge diagnoses more than doubled from approximately 139,000 to 336,600, and the number with a primary CDI diagnosis more than tripled, from 33,000 to 111,000 from 2000 to 2009. This rise in incidence and severity of the disease is possibly associated with the emergence of the hypervirulent strain (NAPI/ribotype 027). CDI is responsible for a spectrum of infections including uncomplicated diarrhea, pseudomembranous colitis, and toxic megacolon, which may lead to sepsis and even death. It often occurs in patients in health-care settings where antibiotics are prescribed and symptomatic patients are concentrated. The most common risk factor for CDI is the use of broad spectrum antibiotics or the concomitant use of multiple and prolonged antimicrobials. Other risk factors include advanced age (65 years or older), recent organ transplantation, gastrointestinal surgery, inflammatory bowel disease, immunosuppressive drugs, presence of multiple co-morbidities, and others. Mature colonic bacterial microbiota (community of micro-organisms) in a healthy adult is generally resistant to C difficile colonization. Any factor altering the balance of intestinal microbiota leads to a selective advantage and colonization by C difficile colonization after exposure to the bacteria.
The standard treatment for C. difficile associated disease includes discontinuation of offending/inducing antibiotic and treatment with metronidazole or vancomycin. Most patients initially respond to this therapy, but 15-30% experience a symptomatic recurrence after discontinuation of the treatment. The risk of recurrence rises to 40% after a first recurrence and to more than 60% after two or more recurrences. The increased incidence and severity of CDI, and the high recurrence rate with conventional treatments have led researchers to explore alternative strategies and therapies with varying degrees of success. These include the use of additional courses of metronidazole and vancomycin, pulsed/tapered antibiotics, the use of new drugs as nitazoxanide and fidaxomicin, immune therapy such as IV immunoglobulin, active immunization, toxin binding, and alternative approaches as the use of probiotics (such as lactobacillus species, which is a low-virulent microorganism that could compete with C difficile for nutrients and sites of mucosal adherence), and fecal transplantation to recreate the colonic environment (Brandt 2012, Guo 2012, Kassam 2011, 2013).

Fecal transplantation (FT), also known as fecal microbiota transplantation (FMT), fecal bacteriotherapy, fecotherapy, fecal microbiota reconstitution, or human probiotics infusion, refers to the process of instilling a liquid suspension of stool from a healthy donor into the gastrointestinal (GI) tract of another person, theoretically to promote normalization of flora and restore the intestinal microbiota. It is of particular utility in recurrent or refractory C difficile infection. The exact mechanism of FMT in treating CDI is not clear, but may involve the re-colonization of microbiota with missing components to generate colonization resistance or direct antagonistic activity of the normal microbiota to C difficile. There is also the possibility that the transplantation of donated flora results in an immunological response facilitating the eradication of C difficile. The re-establishment of the normal composition of the intestinal flora by the use of human fecal microbiota was first used by Ben Eiseman in 1958 for the treatment of four patients with pseudomembranous colitis. Lately, FMT has received more attention with the publication of promising results of case series. It is however, not widely accepted as a therapeutic tool due to lack of published trials with long-term outcomes and concerns regarding its safety and acceptability (Guo 2012, Matilla 2012).

There is no clear definition of CDI, its recurrence, relapse or re-infection, and there is no standardized protocol for FMT as regards the choice of donor (family member or volunteer donor), screening of donors, quantity and preparation of stools collected, form of infusion, and measurement of outcomes. There is also no consensus on the most appropriate form of delivery for the fecal microbiota. Until 1989 retention enema was the most common route for FMT; subsequently it was infused via nasogastric tube, colonoscopy and more recently self-administered enemas. The colonoscopic approach seems to be the most common and favored approach as it allows the examination of the disease extent and inoculation of the entire colon and ileum. Regardless of the delivery method, the steps of the procedure are similar and include evaluating the patient eligibility, patient consent, identification and screening of donors, preparation of the sample, and infusion of the suspension prepared. Donor stool is most often used within 8 hours of passage, but frozen samples have been thawed and used 1-8 weeks after passage. Stool is commonly suspended in saline; however water, milk, and yogurt have also been used as diluents. The suspension is filtered through gauze pads or strainer, and then aspirated into syringes for use. The volume of stool suspension used for FMT varied between studies from less than 200 ml to 500 ml or more. Patients undergoing FMT typically remain on their CDI antimicrobials until 2-3 days prior to the procedure. Bowel preparation is performed regardless of the route. If infused via nasogastric tube, the suspension is applied after fitting the tube in place. After the infusion the tube is rinsed with saline solution and removed. If applied via colonoscopy, the colonoscope is inserted and advanced to the terminal ileum, and then working backwards the stool suspension is administered, most in the terminal ileum and ascending colon. The aftercare requires regular clinical checkups and testing the stools for C difficile. The risk of the procedure includes risks associated with application as perforation and hemorrhage, as well as the risk of microbial translocation and sepsis. FMT is relatively contraindicated in patients with severe comorbid conditions or those taking immunosuppressants, though such patients have been successfully treated with the fecal transplant (Brandt 2011, Gough 2011, Postigo 2012, Rohlke 2012, Kleger 2013, Aroniadis 2013).

Fecal transplantation is not regulated by FDA, to date, as fecal matter is organic. According to the FDA the complex nature of FMT products presents specific scientific and regulatory challenges. The Center for Biologics Evaluation and Research (CBER), together with the National Institute of Allergy and Infectious Disease (NIAID) are holding a public workshop in May 2013, to facilitate clinical development of FMT.

**Medical Technology Assessment Committee (MTAC)**

**Fecal GI infusion for the Treatment of C. Difficile infection**

**04/15/2013: MTAC REVIEW**

**Evidence Conclusion:** There is some evidence from one small RCT that fecal transplantation has a significantly higher success rate than vancomycin in treating patients with recurrent C difficile infection. Meta-analyses of case series with no control groups also show a high cure rate of recurrent CDI with FMT. There is insufficient evidence...
to determine whether FMT is effective for the treatment of patients with the more virulent strain ribotype 027 C
difficile. There is insufficient evidence to determine the most effective and safe modality for delivering the FMT.

**Articles:** The literature search for studies on fecal transplantation for the treatment of *C difficile* infection revealed
one recent RCT (van Nood 2013), and four systematic reviews (Gough 2011, Guo 2012, Kassam 2013 and Sofi
2013). The latter two pooled the results of the published studies in meta-analyses. Sofi and colleagues analyses
combined the results of case series and case reports, while Kassam and colleagues excluded the small case
series (<10 subjects) and case reports in an attempt to minimize bias. The search also identified a review
comparing nasogastric versus colonoscopic FMT (Postigo 2012), and a protocol for a Cochrane review, which is
still being prepared. van Nood 2013 RCT, and the Kassam and colleagues’ meta-analysis that had a more valid
methodology were selected for critical appraisal: van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of
Lee CH, Yuan Y et al. Fecal Microbiota Transplantation for Clostridium difficile Infection: Systematic Review and

The use fecal GI infusion for the treatment of *C. difficile* infection meets the Kaiser Permanente Medical
Technology Assessment Criteria.

**Oral, capsulized, frozen fecal microbiota transplantation (FMT capsule, G3 OpenBiome) for the
treatment of recurrent or refractory clostridium difficile infection**

**BACKGROUND**

*Clostridium difficile* (*C difficile*) infection (CDI) is one of the most prevalent hospital acquired infections in the
United States and is the leading cause of antibiotic associated diarrhea. The incidence of CDI has increased to an
epidemic level; it has become more severe, more refractory to standard treatment, and more likely to relapse.
According to the CDC, CDI was estimated to have caused almost half a million infections in the United States in
2011, and 29,000 deaths within 30 days of the initial diagnosis. It is believed that the rise in incidence and severity
of the disease may be related to the emergence of the hypervirulent strain of the organism (NAP1/BI/027) that is
particularly associated with higher rates of treatment failure and recurrence (Youngster 2014, Hirsch 2015, CDC
webpage accessed November 2015). CDI is responsible for a spectrum of infections including uncomplicated
diarrhea, pseudomembranous colitis, and toxic megacolon, which may lead to sepsis and even death. It often
occurs in patients in health-care settings where antibiotics are prescribed and symptomatic patients are
concentrated. The most common risk factor for CDI is the use of broad spectrum antibiotics or the concomitant
use of multiple and prolonged antimicrobials. Other risk factors include advanced age (65 years or older), recent
organ transplantation, gastrointestinal surgery, inflammatory bowel disease, immunosuppressive drugs, presence
of multiple co-morbidities, and others. Mature colonic bacterial microbiota (community of micro-organisms) in a
healthy adult is generally resistant to colonization and overgrowth of pathogenic bacteria. Any factor altering the
balance of intestinal microbiota allows pathogens such as *C difficile* to proliferate and dominate the gut ecosystem
CDI includes discontinuation of offending/inducing antibiotic and treatment with metronidazole or vancomycin.
Most patients initially respond to this therapy, but 15-30% experience symptomatic recurrence after discontinuation
of the treatment. It is reported that antibiotics targeting CDI may eradicate the active infection, but do not restore
the long-lasting dysbiosis of the microbiota, which is the major risk factor for relapse. This risk rises to 40% after a
first recurrence and to more than 60% after two or more recurrences. The increased incidence and severity of
CDI, and the high recurrence rate with conventional treatments have led researchers to explore alternative
strategies and therapies with varying degrees of success. These include the use of additional courses of
metronidazole and vancomycin, pulsed/tapered antibiotics, the use of new drugs as nitazoxanide and fidaxomicin,
immune therapy such as IV immunoglobulin, active immunization, toxin binding, and alternative approaches such
as use of probiotics as lactobacillus species, which is a low-virulent microorganism that could compete with *C
difficile* for nutrients and sites of mucosal adherence, and fecal microbiota transplantation (Brandt 2012, Guo
2012, Kassam 2013, Hirsch 2015). Fecal microbiota transplantation (FMT), also known as fecal transplantation
(FT), fecal bacteriotherapy, fecotherapy, fecal microbiota reconstitution, or human probiotics infusion, refers to the
process of transplantation of stools from a healthy individual into the gastrointestinal (GI) tract of the affected
patient, theoretically to promote normalization of flora and restore the intestinal microbiota. It may be particularly
useful in recurrent or refractory *C difficile* infection. The exact mechanism of FMT in treating CDI is not clear, but
may involve the re-colonization of microbiota with missing components to generate colonization resistance or
direct antagonistic activity of the normal microbiota to *C difficile*. There is also the possibility that the
transplantation of donated flora results in an immunological response facilitating the eradication of *C difficile*.
The re-establishment of the normal composition of the intestinal flora by the use of human fecal microbiota was first
used by Ben Eiseman in 1958 for the treatment of four patients with pseudomembranous colitis. Lately, FMT has
received more attention with the publication of promising results of a small RCT and a number of case series (Guo
2012, Matilla 2012, van Nood 2013). There is no standardized protocol for FMT as regards the choice of donor (family member or volunteer donor), screening of donors, quantity and preparation of stools collected, form of infusion, and measurement of outcomes. There is also no consensus on the most appropriate form of delivery for the fecal microbiota. Traditionally FMT has been performed by transplanting a liquid suspension of feces from a related healthy donor into the gastrointestinal tract of the affected patient through nasogastric tube, endoscopy, enema, or colonoscopy. The traditional methods are time-consuming, may be technically challenging, unaesthetic, and not accepted by many patients (Brandt 2011, Gough 2011, Postigo 2012, Rohlike 2012, Kieger 2013, Aroniadis 2013). More recently, orally administered capsules containing cryopreserved fecal-material have been described. The capsules are generally prepared using fecal material harvested from unrelated healthy donors fulfilling strict criteria including screening negative for HIV, hepatitis A, B, and C as well as Treponema pallidum. Fecal matter is collected under sterile conditions, combined with saline, processed, sieved, centrifuged, and mixed again with saline along with glycerol, to protect the biological material from becoming damaged when frozen. The fecal material is then dispensed into double or triple capsules and stored at -80°C (-112°F). The capsules should be kept frozen until the time of administration and ingested as quickly as possible after extraction from the freezer. Capsules may be kept at room temperature for up to 90 minutes for patient comfort and ease of swallowing. Another described method is the immediate freezing and storing of the fecal suspension or slurry in 5 or 10 ml syringes at -80°C then thawing and triple encapsulating it prior to its use. Capsules should never be refrozen, and should be disposed of if not used within 90 minutes. OpenBiome (Boston, MA) a stool bank that created a fecal transplant pill (G3) recommends the intake 30 capsules, swallowed consecutively in a single session for the treatment of CDI (OpenBiome website, Youngster 2014, Hirsch 2015). FMT capsule G3 (OpenBiome) are size 00 (approximately the size of a large multivitamin) and are provided with two placebo test capsules. The patient is asked to ingest one test capsule prior to the start of treatment, under direct observation of the physician, to ensure the patient's ability to swallow. Any clinical concerns suggesting an aspiration risk is an absolute contraindication to capsule administration. Other contraindications include severe complicated CDI, dysphagia, history of gastroparesis, allergy to any of the ingredients, adverse events attributable to a previous FMT, and any condition that the treatment my pose a health risk (OpenBiome website). According to OpenBiome, FMT Capsule G3 may be used as a treatment for C. difficile infection not responsive to standard therapies in accordance with the FDA's guidance on the use of fecal microbiota for transplantation, and in clinical trials under an Investigational New Drug (IND) application.

12/21/2015: MTAC REVIEW
Oral, capsulized, frozen fecal microbiota transplantation (FMT capsule, G3 OpenBiome) for the treatment of recurrent or refractory clostridium difficile infection

Evidence Conclusion: There is a lack of published studies on the use of oral cryopreserved FMT capsules for patients with relapsing or refractory CDI. Currently the literature on oral FMT capsules for patients with relapsing C difficile infection (CDI) consists of two small case series and one case report. Youngster and colleagues (2014) (evidence table 1), evaluated the safety and rate of resolution of diarrhea following the administration of cryopreserved FMT capsules in 20 patients (11-89 years of age) with refractory C. difficile infection. The oral capsulized FMT was prepared from stool samples gathered from healthy adult volunteers who had been comprehensively screened for infectious diseases and avoided eating common allergens for several days before donating. Each patient ingested 15 FMT capsules consecutively each day for two successive days. If their symptoms did not improve within 72 hours, they were offered a second course of treatment with fecal material from the same donor. They were followed-up for 6 months and the primary outcomes were safety and clinical resolution of diarrhea with no relapse at 8 weeks. The results of the study show that after the first 2 days of treatment, 14 of the 20 patients (70%) experienced clinical resolution of diarrhea, defined as less than 3 bowel movements/24 hours, and remained symptom free for 8 weeks. After a second course of treatment, four of the remaining patients became symptom free, resulting in an overall 90% rate of symptom resolution. No serious adverse events were reported. The study was a small observational study with no control or comparison group and relied on patient report on clinical outcomes. Patients with symptomatic improvement were not retested for C difficile. The authors indicated that it was a pilot feasibility study that only provides preliminary data on the safety and effectiveness of this oral capsulized FMT. Hirsch et al, 2015 (Evidence table 2), conducted a chart review of 19 patients treated with orally administered FMT capsules for recurrent CDI. FMT was prepared from stools donated by healthy volunteers unrelated to the recipients. Before receiving the FMT, the patients were required to discontinue any CDI antimicrobial treatment for 24 hours and were given a proton pump inhibitor on the evening and morning prior to the therapy. After a light breakfast, they received 6-22 capsules of FMT under supervision in an outpatient setting and were instructed to sit upright and not eat for an hour after ingesting the capsules. Patients were encouraged to drink 4 oz. of fermented milk product twice daily and to consume pro-biotic nutrients for at least 3 days after the FMT. They were followed-up by phone interviews within 2 days, 3 weeks, and after 90 days to assess the response to the therapy and adverse events. Those with recurrent CDI were retreated with antimicrobial therapy and subsequently offered repeat FMT (approximately 6 weeks after the initial FMT) and followed up for an additional 90 days. The primary outcome was resolution of CDI associated diarrhea without

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relapse assessed at 90 days after the last FMT. 13 of the 19 patients treated (68%) responded to a single course, and four responded to the second course of therapy with a total response rate of 89%. No serious adverse events were reported. The study was a small retrospective case series with no control or comparison group, and relied on patient and family report on clinical outcomes. In addition, the follow-up duration was insufficient to determine the long-term safety and effectiveness of the orally ingested FMT capsules. It is also worth noting that the authors have financial ties to Symbiotic Health Inc. Conclusion: There is insufficient evidence to determine that orally ingested FMT capsules prepared from stools provided by volunteer donors is safe and effective for the treatment of patients with CDI. There is insufficient evidence to determine that orally ingested FMT capsules prepared from stools provided by volunteer donors is safe and effective for the treatment of patients with CDI with the more virulent strain \textit{C difficile} (NAP1/BI/027). There is insufficient evidence to determine the long-term efficacy and safety of orally ingested FMT capsules. Case series may only generate hypothesis and large RCTs with long-term follow up are studies needed to support the observed findings and determine the optimal donor, optimal dose of FMT, long-term safety, and long-term efficacy of cryopreserved oral capsulized FMT.

\textbf{Articles:} The literature search revealed two small cases series (one prospective and one retrospective) and a case report on the use of oral cryopreserved FMT capsules for patients with relapsing CDI. There are no published meta-analyses or randomized controlled trials, to date, that compared the use of the oral FMT capsules to standard therapy or to other traditional methods of delivering FMT for the treatment of refractory or relapsing CDI. The following two case series were critically appraised. Youngster I, Russell G, Pindar C, et al. Oral, capsulized, frozen fecal microbiota transplantation for relapsing \textit{Clostridium difficile} infection. \textit{JAMA}. 2014 Nov 5; 312(17):1772-1778. See \textit{Evidence Table 1}. Hirsch BE, Saraiya N, Poeth K, et al. Effectiveness of fecal-derived microbiota transfer using orally administered capsules for recurrent \textit{Clostridium difficile} infection. \textit{BMC Infect Dis}. 2015 Apr 17; 15:191 See \textit{Evidence Table 2}.

The use of Oral, capsulized, frozen fecal microbiota transplantation (FMT capsule, G3 OpenBiome) for the treatment of recurrent or refractory \textit{clostridium difficile} infection does not meet the \textit{Kaiser Permanente Medical Technology Assessment Criteria}.

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<td>MTAC review was discussed at MPC and approved to adopt criteria for FMT capsule, G3 OpenBiome</td>
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<td>05/02/2017</td>
<td>Revised criteria language so it is specific on how to manage care after two recurrences</td>
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<td>05/02/2017</td>
<td>Adopted KPWA policy for Medicare members</td>
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\textbf{Codes}  
CPT: 44705; G0455