Fecal Microbiota Transplantation

Policy Number: 2.01.92  Last Review: 1/2021
Origination: 5/2015  Next Review: 7/2021

Blue KC has developed medical policies that serve as one of the sets of guidelines for coverage decisions. Benefit plans vary in coverage and some plans may not provide coverage for certain services discussed in the medical policies. Coverage decisions are subject to all terms and conditions of the applicable benefit plan, including specific exclusions and limitations, and to applicable state and/or federal law. Medical policy does not constitute plan authorization, nor is it an explanation of benefits.

When reviewing for a Medicare beneficiary, guidance from National Coverage Determinations (NCD) and Local Coverage Determinations (LCD) supersede the Medical Policies of Blue KC. Blue KC Medical Policies are used in the absence of guidance from an NCD or LCD.

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Fecal Microbiota Transplantation when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Fecal microbiota transplantation may be considered medically necessary for treatment of patients with recurrent *Clostridioides difficile* infection under the following conditions (see Considerations section):

- There have been at least 2 recurrences that are refractory to standard antibiotic treatment

When Policy Topic is not covered
Fecal microbiota transplantation is considered investigational in all other situations.

Considerations
There is a lack of consensus on the number of recurrences that warrants consideration of fecal microbiota transplantation (FMT).
The 2017 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines for *Clostridioides difficile* infection state that patients with multiple recurrences of CDI who have failed to resolve their infection with standard of care antibiotic treatments are potential candidates for FMT.\(^1\) It was the opinion of guideline panelists to have patients try appropriate antibiotics for at least 2 recurrences (ie, 3 CDI episodes) before FMT is considered. The optimal timing between multiple FMT sessions is not discussed in the guidelines. Per the 2017 IDSA and Society for Healthcare Epidemiology of America (SHEA) guidelines for *Clostridioides difficile* infection, a recurrent case occurs within 2 to 8 weeks of the incident case and requires both clinical plus laboratory evidence of disease for diagnosis.

Due to the potential for serious adverse reactions with FMT, the U.S. Food and Drug Administration (FDA) has determined that the following protections are needed for use of FMT:

- Donor screening with questions that specifically address risk factors for colonization with multi-drug resistant organisms (MDROs), and exclusion of individuals at higher risk of colonization with MDROs.
- MDRO testing of donor stool and exclusion of stool that tests positive for MDRO. FDA scientists have determined the specific MDRO testing and frequency that should be implemented.
- Consent for the use of FMT is obtained from the patient or a legally authorized representative in accordance with FDA guidance.\(^2\)

On April 9, 2020, the FDA published additional safety information regarding the potential risk of transmission of SARS-CoV-2 via FMT. Recommendations for additional screening and testing procedures are outlined in this publication.\(^3\)

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>With recurrent</td>
<td>Fecal microbiota transplantation</td>
<td>Standard antibiotic regimens</td>
<td>Symptoms</td>
</tr>
<tr>
<td><em>Clostridioides difficile</em></td>
<td></td>
<td></td>
<td>Change in disease status</td>
</tr>
<tr>
<td>infection refractory to</td>
<td></td>
<td></td>
<td>Treatment-related morbidity</td>
</tr>
<tr>
<td>antibiotic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individuals:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With inflammatory bowel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individuals:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With irritable bowel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individuals:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With pouchitis,</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

\(^1\) guidelines. \(^2\) FDA guidance. \(^3\) Additional safety information.
Fecal microbiota transplantation (FMT) involves the administration of intestinal microorganisms via the transfer of stool from a healthy person into a diseased patient, with the intent of restoring normal intestinal flora. Fecal transplant is proposed for treatment-refractory *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI) and other conditions, including inflammatory bowel disease.

For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT, the evidence includes systematic reviews with meta-analyses and observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Meta-analyses have found that FMT is more effective than standard treatment or placebo for patients with recurrent CDI. A long-term prospective study found that FMT for recurrent or refractory CDI appears to be durable at 4 to 8 years following treatment, even for patients who had subsequently received non-CDI antibiotic therapy. A meta-analysis comparing several routes of FMT delivery for the treatment of recurrent CDI found that cure rates were significantly higher with colonoscopy or oral capsules versus nasogastric tube or enema, while colonoscopy and capsules were equally effective. Similar success rates have been demonstrated with FMT using fresh versus frozen feces. Conversely, data regarding the superiority of FMT using donor versus autologous feces are conflicting. Few treatment-related adverse events have been reported. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have irritable bowel disease who receive FMT, the evidence includes systematic reviews and RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Two systematic reviews with meta-analysis concluded that FMT had shown promise in treating patients with ulcerative colitis, but 1 meta-analysis recommended caution about using FMT to treat patients with Crohn disease. A 48-week RCT in patients with ulcerative colitis in clinical remission after prior FMTs found conflicting results for remission outcomes with additional courses of FMT. This current evidence is not sufficient to permit conclusions on the efficacy of FMT for ulcerative colitis. Additionally, questions remain about the optimal route of administration, donor characteristics, and the number of transplants. A small RCT in patients with Crohn disease failed to find a difference in the achievement of remission with FMT versus placebo. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have irritable bowel syndrome who receive FMT, the evidence includes a systematic review and RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The systematic review with meta-analysis reviewed 5 RCTs and reported mixed outcomes for FMT in patients...
with irritable bowel syndrome. When all studies were pooled, no net benefit was found for active FMT. In a pooled analysis of 3 RCTs utilizing autologous FMT as a placebo, patients were less likely to experience an improvement in IBS symptoms with donor FMT (ie, active treatment). Two additional RCTs published after the meta-analysis also utilized autologous FMT as a placebo, and did not find a significant reduction in symptoms of irritable bowel syndrome using donor FMT; both trials also found reduced durability of response 1 year following donor FMT. Few treatment-related adverse events have been reported. Data are limited by small study sizes and heterogeneity in utilized outcome measurement scales and definitions of treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have pouchitis, constipation, multidrug-resistant organism infection, or metabolic syndrome who receive FMT, the evidence includes systematic reviews and an RCT. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Systematic reviews of data from patients who received FMT for constipation, pouchitis, multidrug-resistant organisms, and metabolic syndrome have all concluded that more data are needed before FMT can be applied in clinical practice for these populations. In a meta-analysis assessing the use of FMT in obese and metabolic syndrome patients, the initial improvements of several metabolic parameters failed to demonstrate sustained durability at 12 weeks after treatment. An RCT comparing FMT to no intervention in patients with multidrug-resistant organisms failed to demonstrate improved rates of decolonization with treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

Fecal Microbiota

Fecal microbiota transplantation (FMT), also called donor feces infusion, intestinal microbiota transplantation, and fecal bacteriotherapy involves the duodenal infusion of intestinal microorganisms via the transfer of stool from a healthy individual into a diseased individual to restore normal intestinal flora. The stool can be infused as a liquid suspension into a patient’s upper gastrointestinal tract through a nasogastric tube or gastroscopy, or 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 performs 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

**Clostridioides difficile Infection**

To date, the major potential clinical application of FMT is in the treatment of *Clostridioides difficile* infection (CDI). Infection of the colon with *C. difficile* is a major cause of colitis and can cause life-threatening conditions including colonic perforation and toxic megacolon. *C. difficile* occurs naturally in the intestinal flora. According to the 2019 Centers for Disease Control and Prevention (CDC) report, *Antibiotic Resistance Threats in the United States*, CDI continues to be an urgent threat.\(^4\) In 2017, there were an estimated 223,900 cases of CDI in hospitalized patients and an estimated 12,900 CDI-associated deaths. Interestingly, the overall number of cases of healthcare-associated CDI cases has been trending down since 2012 when the number of cases was estimated at 251,400.

It is unclear what causes *C. difficile* overgrowth, but disruption of the normal colonic flora and colonization by *C. difficile* are major components. Disruption of the normal colonic flora occurs most commonly following the administration of oral, parenteral, or topical antibiotics. Standard treatment for CDI is antibiotic therapy. However, symptoms recur in up to 35% of patients, and up to 65% of patients with recurrences develop a chronic recurrent pattern of CDI.\(^5\)

**Other Applications**

Other potential uses of FMT include the treatment of conditions in which altered colonic flora may play a role: inflammatory bowel disease, irritable bowel syndrome, idiopathic constipation, and non-gastrointestinal diseases such as multiple sclerosis, obesity, autism, and chronic fatigue syndrome. However, for these conditions, the contribution of alterations in colonic flora to the disorder is uncertain or controversial.

There is interest in alternatives to human feces that might have the same beneficial effects on intestinal microbiota without the risks of disease transmission. In a proof of principle study, Petrof et al (2013) evaluated a synthetic stool product in 2 patients with recurrent CDI.\(^6\) The product is made from 33 bacterial isolates developed from culturing stool from a healthy donor.

**Regulatory Status**

In 2016, the U.S. Food and Drug Administration (FDA) issued updated draft guidance on investigational new drug requirements for the use of FMT to treat CDI not responsive to medication therapy.\(^2\) The draft guidance is similar to the 2013 guidance and states that the 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. The 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 the use of fecal transplant for treating conditions other than treatment-resistant CDI.

In 2019, the FDA issued a safety alert regarding the use of FMT due to the potential risk of serious or life-threatening infections caused by the transmission of multi-drug resistant organisms (MDROs). Two immunocompromised individuals received investigational FMT and developed invasive infections caused by the transmission of extended-spectrum beta-lactamase-producing Escherichia coli. One of the affected individuals died. The donor stool used in each patient's FMT procedures had not been tested for extended-spectrum beta-lactamase-producing gram-negative organisms prior to use. Follow-up testing verified donor stool was positive for MDROs identical to the organisms isolated from the 2 patients. Due to these events, the FDA has determined that the following additional protections are required for any investigational use of FMT:

- Donor screening that specifically addresses risk factors for colonization with MDROs and exclusion of individuals at higher risk of colonization with MDROs (eg, health care workers, persons who have recently been hospitalized or discharged from long-term care facilities, persons who regularly attend outpatient medical or surgical clinics, and persons who have recently engaged in medical tourism).
- MDRO testing of donor stool and exclusion of stool testing positive for MDROs. At a minimum, tests should include:
  - extended-spectrum beta-lactamase-producing Enterobacteriaceae
  - vancomycin-resistant enterococci
  - carbapenem-resistant Enterobacteriaceae
  - methicillin-resistant Staphylococcus aureus
- All FMT products currently in storage for future use must be quarantined until donor MDRO carriage risk can be assessed and FMT products are tested and found negative for MDROs.
- The informed consent process for FMT treatment subjects should describe the risk of MDRO transmission and infection and the measures being implemented for donor screening and stool testing.

**Rationale**

The evidence review was created in May 2014 and has been updated regularly with searches of the PubMed. The most recent literature update was performed through October 8, 2020.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.
To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Recurrent *Clostridioides difficile* Infection**

**Clinical Context and Therapy Purpose**
The purpose of fecal microbiota transplantation (FMT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with recurrent *Clostridioides difficile* infection (CDI) refractory to antibiotic therapy.

The question addressed in this evidence review is: Does the use of FMT improve the net health outcome in patients with recurrent CDI?

The following PICO was used to select literature to inform this review.

**Populations**
The relevant population of interest is individuals with recurrent CDI refractory to antibiotic therapy.

**Interventions**
The therapy being considered is FMT. Patients with recurrent CDI are actively managed by gastroenterologists, infectious disease specialists, and primary care providers in an inpatient setting.

**Comparators**
The following therapy is currently being used to treat CDI: standard antibiotic regimens.

**Outcomes**
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Follow-up ranging up to and beyond 12 weeks is of interest to monitor for outcomes. Outcomes reported in FMT trials for CDI include clinical cure, resolution of CDI with no further recurrence, or reduced risk of CDI recurrence. There are inconsistencies across these trials in how CDI resolution (ie, treatment success) and recurrence are defined and measured.\textsuperscript{8,9}
success generally required a resolution of diarrhea symptoms with or without laboratory confirmation; up to 3 consecutive negative stool tests for *C. difficile* toxin have been required to define cure in 1 trial. Conversely, recurrence generally required the presence of diarrhea with or without laboratory confirmation or the need for further treatment for up to 17 weeks after the incident case. The 2017 Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines for CDI recommend against repeat testing for *C. difficile* toxin during the same episode of diarrhea or for asymptomatic patients, since >60% of patients may remain positive for the *C. difficile* toxin even after successful treatment.\(^1\) Per the guidelines, a recurrent case occurs within 2 to 8 weeks of the incident case and requires both clinical plus laboratory evidence of disease for diagnosis.

**Study Selection Criteria**
Methodologically credible studies were selected for the indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

**Review of Evidence**

**Systematic Reviews**
Rokkas et al (2019) performed a systematic review and meta-analysis to assess the efficacy of FMT for the treatment of recurrent CDI.\(^9\) Six RCTs were included in the analysis (N=348), and 7 interventions were compared (donor FMT [dFMT], autologous FMT [aFMT], vancomycin, vancomycin plus dFMT, vancomycin plus bowel lavage, fidaxomicin, and placebo). The primary outcome was the resolution of CDI-related symptoms. The network meta-analysis demonstrated that dFMT was superior to vancomycin (odds ratio [OR], 20.02; 95% credible interval [CrI], 7.05 to 70.03), vancomycin plus dFMT (OR, 4.69; 95% CrI, 1.04 to 25.22), vancomycin plus bowel lavage (OR, 22.77; 95% CrI, 4.34 to 131.63), and fidaxomicin (OR, 22.01; 95% CrI, 4.38 to 109.63) groups.

Tariq et al (2019) performed a systematic review and meta-analysis to assess the efficacy of FMT as a treatment option for recurrent CDI on the basis of results from open-label studies and placebo-controlled clinical trials.\(^8\) The authors were motivated to perform this analysis based on observations that FMT cure rates for CDI are high in observational studies (eg, >90%) but appear to be consistently lower in open-label studies and clinical trials. Thirteen studies were included for evaluation, including 6 placebo-controlled RCTs and 7 open-label studies. Out of 610 patients receiving FMT, 439 patients achieved clinical cure (76.1%; 95%
confidence interval [CI]: 66.4% to 85.7%); study heterogeneity was significant ($I^2 = 91.35\%$). Cure rates were found to be lower in randomized trials (139/216, 67.7%; 95% CI: 54.2% to 81.3%) versus open-label studies (300/394, 82.7%; 95% CI: 71.1% to 94.3%; p<0.001). Subgroup meta-analysis by FMT route of administration indicated lower cure rates with enema than colonoscopy (66.3% versus 87.4%; p<0.001). However, no differences between colonoscopy and oral delivery routes were detected (87.4% to 81.4%; p=0.17). Lower cure rates were observed for studies that included both recurrent and refractory CDI than those that only included patients with recurrent CDI (63.9% versus 79%; p<0.001).

Khan et al (2018) conducted a systematic review of the literature and meta-analysis of pooled data on the use of FMT as a treatment option for recurrent CDI. Reviewers only selected RCTs comparing FMT (fresh or frozen) with medical treatment. Among the selected studies, there was a nonsignificant trend toward the resolution of diarrhea following a single fresh FMT infusion compared with frozen FMT or medical treatment (OR, 2.45; 95% CI, 0.78 to 7.71; p=0.12, $I^2=69\%$), but different forms and routes of FMT administration were shown to be equally efficacious. Reviewers concluded that FMT is a promising treatment modality for recurrent CDI. Variability of FMT dose usages, small trial populations, and window to assess treatment success or failure limited analysis data.

Quraishi et al (2017) published a systematic review and meta-analysis of studies (including RCTs) investigating the effect of FMT in patients with recurrent or refractory CDI. Reviewers deemed the 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 the trials examining the efficacy of FMT were truly placebo-controlled, and the case series followed patients until resolution of CDI (range, 10 weeks to 8 years), though some had an incomplete follow-up. In the pooled analysis, 92% of patients had a resolution of CDI (95% CI, 89% to 94%); heterogeneity was 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 ranged from 68% to 100%.

The Quraishi et al (2017) 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 among studies was considerable.

Prior to the availability of RCTs in this arena, several systematic reviews of uncontrolled studies on FMT for treating CDI were also published. Overall, data from these uncontrolled studies have reported high rates of resolution of recurrent CDI following treatment with FMT.

Table 1 summarizes the characteristics of selected systematic reviews.

### Table 1. Characteristics of Systematic Reviews

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rokkas et al (2019)</td>
<td>To 2018</td>
<td>6</td>
<td>Recurrent CDI treated with FMT, standard of care therapies, or placebo</td>
<td>348</td>
<td>Open-label and blinded RCTs</td>
<td>8 to 17 weeks</td>
</tr>
<tr>
<td>Tariq et al (2019)</td>
<td>To 2017</td>
<td>13</td>
<td>Recurrent or refractory CDI treated with FMT or placebo</td>
<td>Total: 768 (20 to 179) FMT: 610 (16 to 179) Placebo: 157 (14 to 44)</td>
<td>Open-label, randomized trials with no control group, and placebo-controlled RCTs</td>
<td>NR to 17 weeks</td>
</tr>
<tr>
<td>Khan et al (2018)</td>
<td>To 2018</td>
<td>7</td>
<td>Recurrent CDI treated with FMT</td>
<td>543 (20 to 178)</td>
<td>RCTs</td>
<td>NR</td>
</tr>
<tr>
<td>Quraishi et al (2017)</td>
<td>To 2016</td>
<td>37</td>
<td>Recurrent or refractory CDI treated with FMT</td>
<td>3518 (NR)</td>
<td>7 RCTs, 30 case series</td>
<td>10 weeks to 8 years</td>
</tr>
</tbody>
</table>

CDI: Clostridioides difficile infection; FMT: fecal microbiota transplantation; NR: not reported; RCT: randomized controlled trial.

### Retrospective Studies

Investigating the long-term clinical outcomes of FMT in patients with CDI, Mamo et al (2018) conducted a retrospective study using a follow-up survey of 137 patients who had received FMT for recurrent CDI at a single-center between January 2012 and December 2016. Median time from last FMT to follow-up was 22 months. Overall at follow-up, 82% (113/137) of patients had no recurrence of CDI (nonrecurrent CDI group) and 18% (24/137) of patients had CDI (recurrent CDI group). The survey results suggested that antibiotic exposure for non-CDI infections after FMT were more common in the recurrent CDI group (75%) than in the nonrecurrent CDI group (38%; p<0.001). Overall, 82% of patients reported being symptom-free.

In another retrospective study, Meighani et al (2017) assessed outcomes from FMT for recurrent CDI in patients with inflammatory bowel disease (IBD). All
patients underwent FMT between December 2012 and May 2014 within a single health care system. Demographic and clinical characteristics, as well as treatment outcomes for patients with IBD, were compared with those of the general population within this system. Of 201 patients who underwent FMT, 20 had concurrent IBD, and the study found that the response to FMT and CDI relapse rate in the IBD group (n=20) did not differ statistically from the rest of the cohort (n=201). The overall response rate in the IBD population was 75% at 12 weeks. Study design, lack of a standardized FMT treatment protocol, and variable donors limit certainty in conclusions drawn from these data.

**Pediatric Populations**

To characterize a pediatric population with recurrent CDI, Alrdich et al (2018) published a retrospective study that included both hospital-acquired CDI and community-acquired CDI cases, comparing the success rates of various treatments used including FMT.18, The pediatric population consisted of 175 subjects ages 1 to 21 years reporting 215 separate CDI episodes. Treatments included oral metronidazole (145/207 [70%]) and oral vancomycin (30/207 [15%]), with recurrent rates of 30% (42/145) and 37% (11/30), respectively. Overall, 29% (63/215) of all CDI cases had at least 1 documented recurrence. Using multivariate analysis, the study showed that subjects with hospital-acquired CDI were 2.6 times less likely to recur than those with community-acquired CDI (OR, 0.39; 95% CI, 0.18 to 0.85; p=0.018) and that FMT had an overall success rate of 83% (10/12).

**Procedural Approaches**

**Route of Administration**

**Systematic Reviews**

A systematic review and meta-analysis by Ramai et al (2020) compared several routes of FMT delivery for the treatment of recurrent CDI.19, Twenty-six studies (N=1309) were included; colonoscopy was used in 16 studies (n=483), nasogastric/nasoduodenal tube in 5 studies (n=149), enema in 4 studies (n=360), and oral capsules in 4 studies (n=301). The pooled cure rates for colonoscopy, capsules, enema, and nasogastric/nasoduodenal tube were 94.8%, 92.1%, 87.2%, and 78.1%, respectively. Cure rates were significantly higher with colonoscopy versus nasogastric tube or enema (p<0.001 for both); capsules were also superior to nasogastric tube (p<0.001) and enema (p=0.005). The difference in cure rates did not reach statistical significance when comparing colonoscopy and capsules (p=0.126).

The review by Quraishi et al (2017), discussed previously, included a subgroup analysis of FMT delivery.11, 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 the delivery route.
Randomized Controlled Trials

An RCT by Youngster et al (2014) compared the infusion of donor stools administered by colonoscopy or nasogastric tube. Twenty patients with relapsing and recurrent CDI were included. Patients had to have a CDI relapse 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 received donor FMT and were randomized to 1 of 2 infusion routes: a colonoscopy or a nasogastric tube. Both groups received thawed inoculum 90 mL. Patients could receive a second FMT if symptoms did not resolve following the initial transplant. The primary efficacy outcome was a clinical cure, defined as resolution of diarrhea (ie, <3 bowel movements per 24 hours) while off antibiotics for CDI, without relapse for 8 weeks. Fourteen patients were cured after the first FMT, 8 in the colonoscopy group and 6 in the nasogastric tube group; the difference between groups was not statistically significant (p=0.628). Of the remaining 6 patients, 1 refused additional treatment and the other 5 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 other 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 a nasogastric tube.

Fresh Versus Frozen Feces

Systematic Reviews

The review by Ramai et al (2020), discussed previously, included a subgroup analysis of FMT preparation. The overall cure rates were similar amongst patients treated with FMT that used fresh (n=556) versus frozen (n=753) stool (94.9% and 94.5%, respectively).

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

Randomized Controlled Trials

A double-blind RCT by Lee et al (2016) compared fresh with frozen stool used in FMT to treat patients with recurrent CDI. A total of 232 patients were included, with 114 assigned to frozen FMT and 118 to fresh FMT. The primary endpoint was the proportion of patients with no recurrence of CDI-related diarrhea 13 weeks after FMT. The trial was designed as a noninferiority trial, with a margin of 15%. In the per-protocol population (n=178), clinical resolution of symptoms was reported in 76 (83.5%) of 91 patients 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 not reached). In the modified intention-to-treat group, clinical resolution with up to 2 FMT treatments was reported in 81 (75.0%) of 108 patients 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 not reached). The difference between groups was within the 15% noninferiority margin and thus frozen FMT was considered noninferior to fresh FMT.

Donor Versus Autologous Feces

Systematic Reviews
The review by Ramai et al (2020) also included a subgroup analysis of donor relation. Results demonstrated that cure rates were not significantly influenced by whether FMT used unrelated or a mix of related and unrelated donors (94.5% and 95.7%, respectively).

The review by Rokkas et al (2019), discussed previously, included a subgroup analysis of donor relation. Using data from a single RCT, results demonstrated the superiority of dFMT over aFMT for resolution of CDI symptoms (OR, 6.42; 95% CrI, 1.28 to 57.74). The wide CrI creates uncertainty regarding the difference between these interventions.

Long-term Outcomes
Lee et al (2019) performed a prospective study assessing the long-term durability and safety of FMT for patients with recurrent or refractory CDI. Ninety-four patients underwent FMT via retention enema between 2008 to 2012; 32 patients were unreachable and 37 were deceased 4 to 8 years later for a follow-up survey. Twenty-three of the remaining 25 patients completed the questionnaire. No CDI recurrences were reported in patients treated with FMT. Twelve of 23 participants (52.2%) received at least 1 course of antibiotics for treatment of a condition other than CDI. Nine participants (40.9%) received probiotics. Current health was self-reported as "much better" in 17 patients (73.9%) or "somewhat better" in 3 patients (13.0%). The authors concluded that FMT for recurrent or refractory CDI appears to be durable at 4 to 8 years following treatment, even after receiving non-CDI antibiotic therapy.

Section Summary: Recurrent Clostridioides difficile Infection
For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT, the evidence includes systematic reviews with meta-analyses and observational studies. Meta-analyses have found that FMT is more effective than standard treatment or placebo for patients with recurrent CDI. A long-term prospective study found that FMT for recurrent or refractory CDI appears to be durable at 4 to 8 years following treatment, even for patients who had subsequently received non-CDI antibiotic therapy. A meta-analysis comparing several routes of FMT delivery for the treatment of recurrent CDI found that cure rates were significantly higher with colonoscopy or oral capsules versus nasogastric tube or enema, while colonoscopy and capsules were equally effective. Similar success rates have been demonstrated with FMT using fresh versus frozen
feces. Conversely, data regarding the superiority of FMT using donor versus autologous feces are conflicting. Few treatment-related adverse events have been reported. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Inflammatory Bowel Disease**

**Clinical Context and Therapy Purpose**

The purpose of FMT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with inflammatory bowel disease (IBD).

The question addressed in this evidence review is: Does the use of FMT improve the net health outcome in patients with IBD?

The following PICO was used to select literature to inform this review.

**Populations**

The relevant population of interest is individuals with IBD. Individuals with IBD include subsets of patients with ulcerative colitis (UC) and Crohn disease (CD).

**Interventions**

The therapy being considered is FMT. Patients with IBD are actively managed by gastroenterologists and primary care providers in an outpatient setting.

**Comparators**

The following therapy is currently being used to treat IBD: standard of care.

**Outcomes**

The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Follow-up out to 12 weeks is of interest to monitor for outcomes. In clinical trials of FMT for CD or UC, there are inconsistencies in reported outcomes. Clinical remission was the most commonly reported outcome, but study definitions varied.

According to the 2019 American Gastroenterological Association guidelines for moderate to severe UC, the following outcomes should be used for decision-making for adults with moderate to severe UC²³.

- Induction and maintenance of remission
- Short-term colectomy risk (within 3 months of hospitalization)

Other important outcomes recognized by these guidelines include:

- Induction and maintenance of endoscopic remission
- Maintenance of corticosteroid-free remission
- Serious adverse events (including serious infections and malignancy)
- Treatment tolerability (drug discontinuation due to adverse events)
According to the 2018 American Gastroenterological Association guidelines for CD, common outcomes in clinical trials of CD patients include measurements of Crohn's disease activity index (CDAI), the Harvey Bradshaw Index, and other patient-reported outcome tools. With regard to remission, the guidelines stress that patients with CD may be in histologic, endoscopic, clinical, or surgical remission. The guidelines note there has been a recent push to more patient-reported outcomes and objective measures of disease (endoscopy findings) versus CDAI. Mucosal healing is an important target in assessing the efficacy of therapies for IBD. In this population, mucosal healing is defined as an absence of ulceration. Endoscopic scoring systems have been developed to quantify the degree of ulceration and inflammation in patients with CD. The Simple Endoscopic Score for Crohn's disease (SES-CD) has been used to assess endoscopic activity in clinical practice.

**Review of Evidence**

**Systematic Reviews**

A systematic review and meta-analysis by Zhou et al (2020) searched for studies to September 2019 evaluating the efficacy and safety of FMT, biological agents, and tofacitinib in patients with UC. Sixteen RCTs were identified (4 with FMT, 10 with biological agents, and 2 with tofacitinib). Compared with the placebo, the clinical response was significantly higher with FMT (RR, 1.648; 95% CI, 1.253 to 2.034) as was clinical remission (RR, 2.486; 95% CI, 1.393 to 4.264). Indirect comparisons did not reveal any statistically significant differences between FMT and adalimumab, infliximab, golimumab, vedolizumab, or tofacitinib for either clinical response or clinical remission. The incidence of adverse events was also similar when comparing FMT to biologics or tofacitinib.

A systematic review and meta-analysis by Paramsothy et al (2017) searched for studies to January 2017 evaluating the efficacy and/or safety of FMT use in treating IBD, distributed across 3 disease subtypes (UC, CD, and pouchitis). Fifty-three studies were selected and analyzed for this review (41 in UC, 11 in CD, 4 in pouchitis). Overall, 36% (201/555) of UC patients, 50.5% (42/83) of CD patients, and 21.5% (5/23) of pouchitis patients achieved the primary outcome of clinical remission. Pooled proportion achieving clinical remission was 33% among cohort studies, with a moderate risk of heterogeneity; among the 4 RCTs selected, there was a significant benefit in clinical remission (OR, 2.89; 95% CI, 1.36 to 6.13; p=0.006), with moderate heterogeneity. Transient gastrointestinal complaints comprised most of the adverse events. Reviewers concluded that FMT appeared most promising in treating UC, and the use of FMT to treat CD should be interpreted cautiously, due to wide CIs.

Sha et al (2014) published a systematic review of observational data on FMT for the treatment of IBD. Reviewers identified reports of 111 IBD patients (UC and CD) worldwide who received fecal transplants for IBD. All studies were case series. Remission was achieved in 87 (77.8%) of 111 IBD patients.
Randomized Controlled Trials
Sokol et al (2020) published the results of a small, multicenter, single-blind, placebo-controlled RCT in France investigating endoscopic delivery of FMT in patients with CD. Patients could not be on concomitant tumor necrosis factor inhibitors, and those with active disease at screening were treated with oral prednisone. Only those patients who achieved clinical remission within the 3 weeks following the commencement of corticosteroids (defined as a Harvey Bradshaw Index <5) were randomized to treatment or placebo. The treatment group received FMT after colon cleansing with polyethylene glycol. The primary endpoint was the colonization of donor microbiota at week 6. Colonization was defined as being successful if the fecal microbiota of the recipient 6 weeks after FMT was more similar to the fecal microbiota of the donor than to the recipient before FMT; similarity was assessed using Sorensen’s index, and a score ≥0.6 signaled successful colonization. The rate of clinical flares in the 24 weeks following FMT was a secondary endpoint in the study. A clinical flare was defined as any 1 of the following: a CDAI > 220 points, a CDAI between 150 and 220 with an increase >70 compared with baseline, the need for surgery, or the need to start a new medical treatment for CD. Eight patients received FMT and 9 received placebo treatment. None of the adverse events observed in the trial were considered to be related to FMT.

Sood et al (2019) published results of a 48-week small single-center RCT in India evaluating maintenance FMT (n=31) versus placebo (n=30) in patients with UC receiving standard of care therapies who are in clinical remission after prior FMT sessions. The primary endpoint was the maintenance of steroid-free clinical remission (Mayo score ≤2 and all subscores ≤1) at week 48. Relapse occurred in 3 patients in the FMT group and 8 patients in the placebo group. There were no serious adverse events reported in this trial.

Tables 2 and 3 summarize the characteristics and results of selected RCTs. Tables 4 and 5 summarize the study relevance, design, and conduct limitations.

Table 2. Summary of Key Randomized Controlled Trial Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Active</td>
<td>Comparator</td>
</tr>
<tr>
<td>Sokal et al (2020) 28.</td>
<td>France</td>
<td>6</td>
<td>2014 to 2017</td>
<td>8; FMT using</td>
<td>n=9; vehicle physiological serum administered in the cecum during colonoscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50 to 100 g of fresh donor stool resuspended in 250 to 350 ml of sterile sodium chloride, filtered, and administered in the cecum during colonoscopy</td>
<td></td>
</tr>
<tr>
<td>Sood et al (2019) 29.</td>
<td>India</td>
<td>1</td>
<td>2015 to</td>
<td>31; FMT using</td>
<td>n=30; preservative free normal saline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2017</td>
<td>100 g of fresh donor</td>
<td></td>
</tr>
</tbody>
</table>
2017 remission (Mayo score ≤ 2 and each subscore of ≤ 1) after prior FMTs stool resuspended in 200 ml of sterile sodium chloride, filtered, and administered via retention enema (4 to 6 hours) every 8 weeks; standard of care UC therapies were allowed with food-grade color via retention enema (4 to 6 hours) every 8 weeks; standard of care UC therapies were allowed

CDI: *Clostridioides difficile* infection; FMT: fecal microbiota transplantation; NL: Netherlands; NR: not reported; UC: ulcerative colitis.

**Table 3. Summary of Key Randomized Trial Results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome, n (%)</th>
<th>Active</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokol et al (2020)²⁸</td>
<td>Successful colonization¹</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Flare-free survival at week 24²</td>
<td>5 (62.5)</td>
<td>3 (33.3)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p=0.23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Steroid-free clinical remission at Week 10³</td>
<td>7 (87.5)</td>
<td>4 (44)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p=0.13</td>
<td></td>
</tr>
<tr>
<td>Sood et al (2019)²⁹</td>
<td>Steroid-free clinical remission at week 48⁴</td>
<td>21 (87.1)</td>
<td>20 (66.7)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p=0.111</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endoscopic remission at week 48⁵</td>
<td>18 (58.1)</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p=0.026</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histological remission at week 48⁶</td>
<td>14 (45.2)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p=0.033</td>
<td></td>
</tr>
</tbody>
</table>

dFMT: donor fecal microbiota transplantation

¹Colonization was defined as being successful if the fecal microbiota of the recipient 6 weeks after FMT was more similar to the fecal microbiota of the donor than to the recipient before FMT; similarity was assessed using Sorensen’s index, and a score ≥0.6 signaled successful colonization.

²A clinical flare was defined as any 1 of the following: a CDAI > 220 points, a CDAI between 150 and 220 with an increase >70 compared with baseline, the need for surgery, or the need to start a new medical treatment for CD.

³Steroid-free clinical remission was not explicitly defined by authors.

⁴Steroid-free clinical remission was defined as Mayo score ≤ 2 and sub scores ≤ 1

⁵Endoscopic remission was defined as Mayo score 0

⁶Histological remission was defined as Nancy grade 0 or 1

**Table 4. Study Relevance Limitations**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokol et al (2020)²⁸</td>
<td>N=8 (dFMT)</td>
<td>N=9 (placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sood et al (2019)²⁹</td>
<td>N=31 (dFMT)</td>
<td>N=30 (placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Allocationa</td>
<td>Blindingb</td>
<td>Selective Reportingc</td>
<td>Data Completenessd</td>
<td>Powere</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>----------------------</td>
<td>-------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Sokol et al (2020)28</td>
<td>1, 2. investigators were not blinded to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FMT: fecal microbiota transplantation
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokol et al (2020)28</td>
<td>1, 2. investigators were not blinded to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FMT: fecal microbiota transplantation; NCT: national clinical trial.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. No intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Long-Term Outcomes
Li et al (2020) published the results of a prospective observational cohort study that included 202 patients with UC who underwent the first course of FMT at a single center in China between November 2012 to September 2018. Patients with mild, moderate, and severe active UC (Mayo score from 3 to 12) were included. Of the initial 202 patients, 122 patients who achieved clinical response at 1 month after the first course of FMT were included in the analysis for time of maintaining efficacy. Among these 122 patients, 22 patients had a sustained response without undergoing a second course of FMT until January 1, 2019 (the terminal point of follow-up), 77 patients had disease relapse before the second course of FMT, and 23 patients underwent consolidation therapy with a second course of FMT before disease relapse. The median follow-up was 25.5 months (interquartile range [IQR], 11.75 to 43 months). The median time of maintaining efficacy from the first course of FMT in 99 patients was 120 days (IQR, 45 to 180 days) and the median time of maintaining efficacy from the second course (ie, consolidation) of FMT in 23 patients was 415 days (IQR, 255 to 780 days; p<0.001). No new safety issues were reported in this study.

The study by Sood et al (2019), discussed previously, reported results of a 48-week RCT evaluating maintenance FMT (n=31) versus placebo (n=30) in patients with UC receiving standard of care therapies who are in clinical remission after prior FMT sessions. Maintenance of steroid-free clinical remission (Mayo score ≤2 and all subscores ≤1) was numerically higher in patients allocated to FMT (27 patients [87.1%]) versus placebo (20 patients [66.7%]), but the difference did not reach statistical significance (p=0.111). A significantly higher number of patients with FMT versus placebo achieved endoscopic remission (58.1% versus 26.7%; p=0.026) and histological remission (45.2% versus 16.7%; p=0.033). Three patients receiving FMT (9.7%) and 8 patients on placebo (26.7%) relapsed.

Section Summary: Inflammatory Bowel Disease
For individuals who have IBD who receive FMT, the evidence includes systematic reviews and RCTs. Two systematic reviews with meta-analysis concluded that FMT had shown promise in treating patients with UC, but 1 meta-analysis recommended caution about using FMT to treat patients with CD. A 48-week RCT in patients with UC in clinical remission after prior FMTs found conflicting results for remission outcomes with additional courses of FMT. This current evidence is not sufficient to permit conclusions on the efficacy of FMT for UC. Additionally, questions remain about the optimal route of administration, donor characteristics, and the number of transplants. A small RCT in patients with CD failed to find a difference in the achievement of remission with FMT versus placebo. The evidence is insufficient to determine the effects of the technology on health outcomes.

Irritable Bowel Syndrome
Clinical Context and Therapy Purpose
The purpose of FMT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with irritable bowel syndrome (IBS).

The question addressed in this evidence review is: Does the use of FMT improve the net health outcome in patients with IBS?

The following PICO was used to select literature to inform this review.

**Populations**
The relevant population of interest is individuals with IBS. IBS is a gastrointestinal disordered marked by chronic abdominal pain with or without altered bowel movement patterns, in the absence of underlying damage or an identified cause. It is the most commonly diagnosed gastrointestinal condition, accounting for approximately 30% of all gastroenterologist referrals. The clinical prevalence as estimated from population-based studies in North America is approximately 10 to 15%. While the pathophysiology of IBS remains uncertain, the complex ecology of the fecal microbiota has led to speculation whether alterations in its composition could be associated with IBS.

**Interventions**
The therapy being considered is FMT. Patients with IBS are actively managed by gastroenterologists and primary care providers in an outpatient setting.

**Comparators**
The following therapy is currently being used to treat IBS: standard of care. Standard of care may include lifestyle and dietary modifications, the establishment of a physical exercise program, and counseling to manage psychosocial factors. For patients with moderate to severe symptoms that impair quality of life, medication management with various symptom-targeting supplements and/or pharmacologic agents (e.g., soluble fiber, polyethylene glycol, osmotic laxatives, lubiprostone, linaclotide, tegaserod, loperamide, cholestyramine, and others) may be considered. For patients with refractory symptoms despite adjunctive pharmacologic therapy, food allergy testing, behavior modification, and pharmacological management of psychiatric impairment may be considered.

**Outcomes**
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Though not completely standardized, follow-up for IBS would typically occur in the months to years after starting treatment.

Due to the absence of a biologic disease marker, IBS is often difficult to diagnose in the clinical setting. Several symptoms-based criteria have been developed in an effort to standardize the diagnosis of IBS. The most widely used criteria are the Rome IV criteria, which define IBS as recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:
• Related to defecation, with an increase or improvement in pain
• Associated with a change in stool frequency
• Associated with a change in stool form (appearance)

The previous Rome III diagnostic criteria are less restrictive, and are commonly featured in current studies on IBS. The Rome III criteria define IBS as recurrent abdominal pain or discomfort, 3 days per month in the last 3 months (12 weeks), associated with 2 or more of the criteria below:

• Improvement with defecation
• Onset associated with a change in stool frequency
• Onset associated with a change in stool form (appearance)

The Rome III criteria are fulfilled when symptoms have an onset 6 months prior to diagnosis. Subtypes of IBS are based on patient-reported predominant bowel patterns on days with abnormal bowel movements and may utilize the Bristol stool form scale to record stool form and appearance. IBS subtypes defined for clinical practice include:

• IBS with predominant constipation (IBS-C): abnormal bowel movements with predominant constipation (type 1 and 2 on the Bristol stool form scale)
• IBS with predominant diarrhea (IBS-D): abnormal bowel movements with predominant diarrhea (type 6 and 7 on the Bristol stool form scale)
• IBS with mixed bowel habits (IBS-M): >1/4 of abnormal bowel movements constipation and >1/4 of abnormal bowel movements were diarrhea
• IBS unclassified: patients meet diagnostic criteria for IBS but cannot accurately be categorized into 1 of the 3 main subtypes

The Manning criteria is another diagnostic algorithm that may be used in the diagnosis of IBS, consisting of a questionnaire delivered to the patient by the treating clinician to establish the presence of typical symptoms. Positive diagnosis requires that 3 or more of the following symptoms are met:

• Pain relieved with defecation
• More frequent stools at the onset of pain
• Looser stools at the onset of pain
• Visible abdominal distention
• Passage of mucus
• Sensation of incomplete evacuation

A validation study comparing the Manning criteria to a previous version of the Rome criteria found it to have less sensitivity but greater specificity in diagnosing IBS.

Measuring outcomes and severity of illness for patients in IBS can be challenging. The Rome Founding Working Team Report indicates that calculating severity in IBS is a complex matter, and is primarily determined by patient-reported symptoms,
behaviors, and personal experience of illness. Severity must be understood through a broad integration of health-related quality of life, psychosocial factors, healthcare utilization behaviors, and burden of illness. Individual symptoms such as abdominal pain were considered important but insufficient determinants of IBS severity. Two validated severity measurement scales include the Functional Bowel Disorder Severity Index and the IBS Severity Scoring System (IBS-SSS). The Functional Bowel Disorder Severity Index assesses severity based on patient pain behaviors such as the presence and intensity of pain and the number of illness-related healthcare visits. Resultant scores categorize patients with mild (≤36), moderate (37-110) or severe (>110) IBS. The IBS-SSS evaluates the intensity of IBS symptoms during a 10-day period and includes assessments of abdominal pain, distension, stool frequency and consistency, and interference with patient quality of life, with each component graded via a visual analog scale. The IBS-SSS provides scores between 0 and 500 and categorizes patients as having mild (75-175), moderate (175-300), or severe (>300) IBS.

**Review of Evidence**

**Systematic Reviews**

Ianiro et al (2019) performed a systematic review and meta-analysis to examine the efficacy of FMT as a treatment for IBS compared to either inactive placebo or autologous stool placebo. Three RCTs enrolling 267 patients were included for analysis. Only 7.8% of the included patients had IBS-C. After study data were pooled, 79 (50%) of 158 patients assigned to donor FMT failed to respond, whereas 56 (51.4%) of 109 assigned to placebo failed to respond. Further characteristics and results are summarized in Tables 6 and 7. Study outcomes were mixed by both routes of administration and assignment to treatment or placebo. When data from 3 RCTs utilizing autologous FMT as control groups were pooled, patients were more likely to experience an improvement in IBS symptoms with autologous FMT compared to donor FMT. While all studies utilized Rome III criteria for patient diagnosis and enrollment, not all studies utilized a validated IBS severity scoring system to quantify patient outcomes, limiting interpretation of results.

**Table 6. Characteristics of Systematic Reviews**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ianiro et al (2019)</td>
<td>To 2019</td>
<td>5</td>
<td>Patients with IBS, including IBS-D, IBS-C, and IBS-M, diagnosed with Rome III criteria</td>
<td>267 (17-86)</td>
<td>RCTs</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

IBS: irritable bowel syndrome; IBS-C: irritable bowel syndrome with constipation; IBS-D: irritable bowel syndrome with diarrhea; IBS-M: irritable bowel syndrome with mixed constipation and diarrhea; RCT: randomized controlled trial.

**Table 7. Results of Systematic Reviews**

<table>
<thead>
<tr>
<th>Study</th>
<th>IBS Symptoms Not Improving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ianiro et al (2019)</td>
<td></td>
</tr>
</tbody>
</table>
### Overall

<table>
<thead>
<tr>
<th>Number of Patients, N (Trials)</th>
<th>267 (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk (95% CI)</td>
<td>0.98 (0.58-1.66)</td>
</tr>
<tr>
<td>$I^2$ (P-Value)</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Route of Donor FMT Administration

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Number of Patients, N (Trials)</th>
<th>Relative Risk (95% CI)</th>
<th>$I^2$ (P-Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Capsule:</td>
<td>100 (2)</td>
<td>1.96 (1.19 to 3.20)</td>
<td>14% (p = 0.28)</td>
</tr>
<tr>
<td>Colonoscopy:</td>
<td>103 (2)</td>
<td>0.63 (0.43 to 0.93)</td>
<td>0% (p = 0.71)</td>
</tr>
<tr>
<td>Nasojejunal Tube:</td>
<td>64 (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Placebo Type

<table>
<thead>
<tr>
<th>Placebo Type</th>
<th>Number of Patients, N (Trials)</th>
<th>Relative Risk (95% CI)</th>
<th>$I^2$ (P-Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive Placebo:</td>
<td>100 (2)</td>
<td>1.96 (1.19 to 3.20)</td>
<td>14% (0.28)</td>
</tr>
<tr>
<td>Autologous Stool:</td>
<td>167 (3)</td>
<td>0.66 (0.50 to 0.87)</td>
<td>0% (0.89)</td>
</tr>
</tbody>
</table>

CI: confidence interval; NA: not applicable; NR: not reported.

### Randomized Controlled Trials

Holvoet et al (2020) reported the results of a double-blind RCT evaluating the efficacy of FMT in patients with IBS-D or IBS-M and severe bloating (mean abdominal bloating sub-score of $\geq 3$). The intervention group (n=43) received donor FMT via the nasojejunal route and the control group (n=19) received autologous FMT placebo via the same route. A daily symptom diary was used to assess IBS-related symptoms and improvement in IBS symptoms at 12 weeks was the primary outcome of the trial. After a single FMT, more patients in the treatment group versus placebo reported efficacy for more than 1 year (21% versus 5%). A second FMT reduced symptoms in 67% of patients with an initial response to donor stool, but not in patients with a prior non-response.

Lahtinen et al (2020) reported the results of a double-blind RCT evaluating the efficacy of FMT in patients with IBS. The intervention group (n=23) received donor FMT via colonoscopy and the control group (n=26) received autologous FMT placebo via the same route. The primary outcome, a reduction in the IBS-SSS score of at least 50 points at 52 weeks, was not achieved in either study group. While there was a significant reduction in the mean IBS-SSS score in the donor FMT group at 12 weeks after treatment as compared to baseline (p=0.01), the
number of patients achieving a reduction of at least 50 points at this time did not differ (48% with donor FMT versus 42% with autologous FMT placebo). Approximately 35% of patients experienced adverse events with no significant difference between groups.

Characteristics and results of selected studies are summarized in Tables 8 and 9. Study relevance, design, and conduct limitations are summarized in Tables 10 and 11.

### Table 8. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holvoet et al (2020)</td>
<td>Belgium</td>
<td>1</td>
<td>2015 to 2017</td>
<td>n=43; donor FMT using fresh sample resuspended in 300 ml of sterile normal saline, filtered, and administered via nasojejunal route</td>
<td>n=19; autologous FMT placebo via nasojejunal route; 300 ml prepared fresh and stored frozen until treatment</td>
</tr>
<tr>
<td>Lahtinen et al (2020)</td>
<td>Finland</td>
<td>NR</td>
<td>NR</td>
<td>n=23; donor FMT; 30 g donor stool prepared fresh and stored frozen until treatment; delivered via colonoscopy</td>
<td>n=26; autologous FMT placebo prepared fresh; delivered via colonoscopy</td>
</tr>
</tbody>
</table>

IBS: irritable bowel syndrome; FMT: fecal microbiota transplantation; NR: not reported; RCT: randomized controlled trial.

### Table 9. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Response, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holvoet et al (2020)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement of IBS symptoms and bloating at 12 weeks</td>
<td>Donor FMT (43)</td>
<td>Autologous FMT placebo (19)</td>
</tr>
<tr>
<td>Lahtinen et al (2020)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in IBS-SSS score ≥50 points at 12 weeks</td>
<td>Donor FMT (23)</td>
<td>Autologous FMT placebo (26)</td>
</tr>
</tbody>
</table>
Decrease in IBS-SSS score ≥50 points at 52 weeks

| Donor FMT (23) | Autologous FMT placebo (26) | NR | NR | NS |

IBS: irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Symptom Severity Scale; FMT: fecal microbiota transplantation; NR: not reported; NS: not significant; RCT: randomized controlled trial.

Table 10. Study Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Follow-Up²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holvoet et al (2020)³³</td>
<td>4. Rationale for excluding individuals with IBS with constipation was not provided</td>
<td>1. FMT products were not prepared with a standard amount of autologous stool</td>
<td>1. placebo FMT products were not prepared with a standard amount of autologous stool</td>
<td>4. Primary outcome measure was not established and validated measurements; 5. A clinically significant difference was not prespecified for the primary outcome</td>
<td></td>
</tr>
<tr>
<td>Lahtinen et al (2020)³⁴</td>
<td>1. placebo FMT products were not prepared with a standard amount of autologous stool</td>
<td>1. placebo FMT products were not prepared with a standard amount of autologous stool</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

FMT: fecal microbiota transplantation; IBS: irritable bowel syndrome.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 11. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
</table>
Lahtinen et al (2020)\textsuperscript{34},

The number of patients achieving the primary outcome was not reported; confidence intervals and p-values not reported for all outcomes

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

\textsuperscript{a} Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

\textsuperscript{b} Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

\textsuperscript{c} Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

\textsuperscript{d} Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. No intent to treat analysis (per protocol for noninferiority trials).

\textsuperscript{e} Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

\textsuperscript{f} Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: IBS

For individuals who have IBS who receive FMT, the evidence includes a systematic review and RCTs. The systematic review with meta-analysis reviewed 5 RCTs and reported mixed outcomes for FMT in patients with IBS. When all studies were pooled, no net benefit was found for active FMT. In a pooled analysis of 3 RCTs utilizing autologous FMT as a placebo, patients were less likely to experience an improvement in IBS symptoms with donor FMT (ie, active treatment). Two additional RCTs published after the meta-analysis also utilized autologous FMT as a placebo, and did not find a significant reduction in symptoms of IBS using donor FMT; both trials also found reduced durability of response 1 year following donor FMT. Few treatment-related adverse events have been reported. Data are limited by small study sizes and heterogeneity in utilized outcome measurement scales and definitions of treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Pouchitis, Constipation, Multi-Drug Resistant Organism Infection, or Metabolic Syndrome**

**Clinical Context and Therapy Purpose**
The purpose of FMT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with pouchitis, constipation, multidrug-resistant organism (MDRO) infection, or metabolic syndrome.
The question addressed in this evidence review is: Does the use of FMT improve the net health outcome in patients with pouchitis, constipation, MDRO infection, or metabolic syndrome?

The following PICO was used to select literature to inform this review.

**Populations**
The relevant population of interest is individuals with pouchitis, constipation, MDRO infection, or metabolic syndrome.

**Interventions**
The therapy being considered is FMT. Patients with pouchitis, constipation, MDRO infection, or metabolic syndrome are actively managed by gastroenterologists and primary care providers in an outpatient setting.

**Comparators**
The following therapy is currently being used to treat pouchitis, constipation, MDRO infection, and metabolic syndrome: standard of care.

**Outcomes**
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Though not completely standardized, follow-up for pouchitis, constipation, MDRO infection, or metabolic syndrome symptoms would typically occur in the months to years after starting treatment.

**Review of Evidence**

**Systematic Reviews**
A systematic review by Rossen et al (2015) of studies on FMT identified a case series on constipation (n=3 patients) and another on pouchitis (n=8 patients).\(^{35}\). An additional systematic review by Cold et al (2020) evaluating FMT treatment in 69 patients with chronic pouchitis concluded that the use of FMT in this population requires further study before incorporation into clinical practice.\(^{36}\).

A systematic review by Saha et al (2019) identified 21 studies (N=192) on FMT in preventing multidrug-resistant infections and/or its effect on MDRO colonization.\(^{37}\). Only 1 of the studies was an RCT (see Huttner et al summary under Randomized Controlled Trials), 7 were uncontrolled clinical trials, 2 were retrospective cohort studies, and 11 were case series or case reports. The MDRO eradication rate ranged from 0 to 100% using all included data; when excluding data from case series and case reports, the eradication rate ranged from 37.5% to 87.5%. No serious adverse events from FMT were reported. The authors concluded that more data are needed before FMT can be applied in clinical practice as a treatment for eradicating MDR colonization and preventing recurrent MDR infections.
A systematic review and meta-analysis by Proenca et al (2020) searched for RCTs assessing the use of FMT in obese and metabolic syndrome patients. Six RCTs (N=154) were included in the meta-analysis, of which 5 studies assessed the role of FMT for metabolic syndrome in obesity and 1 assessed the role of FMT in obese patients without metabolic syndrome. Two to 6 weeks after intervention, patients in the FMT group had a lower mean concentration of glycated hemoglobin than the placebo group (mean difference [MD], -1.69 mmol/L; 95% CI, -2.81 to -0.56; p=0.003) and higher mean high-density lipoprotein (HDL) cholesterol than the placebo group (MD, 0.09 mmol/L; 95% CI, 0.02 to 0.15; p=0.008); the placebo group had lower mean low-density lipoprotein (LDL) cholesterol than the FMT group (MD, 0.19 mmol/L; 95% CI, 0.05 to 0.34; p=0.008). Fasting glucose, triglycerides, and total cholesterol did not differ between groups after 2 to 6 weeks. At 12 weeks after treatment, there was no statistically significant difference between FMT and placebo for the following outcomes: concentration of glycated hemoglobin, fasting glucose, LDL cholesterol, HDL cholesterol, and triglycerides. The authors concluded that more data are needed before FMT can be applied in clinical practice as a treatment for metabolic syndrome.

Randomized Controlled Trials
An RCT by Huttnner et al (2019) evaluated the superiority of a 5-day course of antibiotic therapy followed by FMT (n=22) for the treatment of MDROs compared to no intervention (n=17). Patients with either extended-spectrum beta-lactamase-producing Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae were enrolled. In the intention-to-treat analysis, 9/22 (41%) of patients assigned to the intervention group were negative for both extended-spectrum beta-lactamase-Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae compared to 5/17 (29%) of patients in the no-intervention control arm at follow-up days 35 to 48. No superior benefit was observed with an odds ratio for decolonization success of 1.7 (95% CI: 0.4 to 6.4).

Section Summary: Pouchitis, Constipation, MDRO Infection, or Metabolic Syndrome
For individuals who have pouchitis, constipation, MDRO infection, or metabolic syndrome who receive FMT, the evidence includes systematic reviews and an RCT. Systematic reviews of data from patients who received FMT for constipation, pouchitis, MDROs, and metabolic syndrome have all concluded that more data are needed before FMT can be applied in clinical practice for these populations. In a meta-analysis assessing the use of FMT in obese and metabolic syndrome patients, the initial improvements of several metabolic parameters failed to demonstrate sustained durability at 12 weeks after treatment. An RCT comparing FMT to no intervention in patients with MDROs failed to demonstrated improved rates of decolonization with treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

Adverse Events
Wang et al (2016) published a systematic review of adverse events associated with FMT. Reviewers identified 50 publications (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 2 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 systematic reviews with meta-analyses and observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Meta-analyses have found that FMT is more effective than standard treatment or placebo for patients with recurrent CDI. A long-term prospective study found that FMT for recurrent or refractory CDI appears to be durable at 4 to 8 years following treatment, even for patients who had subsequently received non-CDI antibiotic therapy. A meta-analysis comparing several routes of FMT delivery for the treatment of recurrent CDI found that cure rates were significantly higher with colonoscopy or oral capsules versus nasogastric tube or enema, while colonoscopy and capsules were equally effective. Similar success rates have been demonstrated with FMT using fresh versus frozen feces. Conversely, data regarding the superiority of FMT using donor versus autologous feces are conflicting. Few treatment-related adverse events have been reported. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have irritable bowel disease who receive FMT, the evidence includes systematic reviews and RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Two systematic reviews with meta-analysis concluded that FMT had shown promise in treating patients with ulcerative colitis, but 1 meta-analysis recommended caution about using FMT to treat patients with Crohn disease. A 48-week RCT in patients with ulcerative colitis in clinical remission after prior FMTs found conflicting results for remission outcomes with additional courses of FMT. This current evidence is not sufficient to permit conclusions on the efficacy of FMT for ulcerative colitis. Additionally, questions remain about the optimal route of administration, donor characteristics, and the number of transplants. A small RCT in patients with Crohn disease failed to find a difference in the achievement of remission with FMT versus placebo. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have irritable bowel syndrome who receive FMT, the evidence includes a systematic review and RCTs. Relevant outcomes are symptoms, change
in disease status, and treatment-related morbidity. The systematic review with meta-analysis reviewed 5 RCTs and reported mixed outcomes for FMT in patients with irritable bowel syndrome. When all studies were pooled, no net benefit was found for active FMT. In a pooled analysis of 3 RCTs utilizing autologous FMT as a placebo, patients were less likely to experience an improvement in IBS symptoms with donor FMT (ie, active treatment). Two additional RCTs published after the meta-analysis also utilized autologous FMT as a placebo, and did not find a significant reduction in symptoms of irritable bowel syndrome using donor FMT; both trials also found reduced durability of response 1 year following donor FMT. Few treatment-related adverse events have been reported. Data are limited by small study sizes and heterogeneity in utilized outcome measurement scales and definitions of treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have pouchitis, constipation, multidrug-resistant organism infection, or metabolic syndrome who receive FMT, the evidence includes systematic reviews and an RCT. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Systematic reviews of data from patients who received FMT for constipation, pouchitis, multidrug-resistant organisms, and metabolic syndrome have all concluded that more data are needed before FMT can be applied in clinical practice for these populations. In a meta-analysis assessing the use of FMT in obese and metabolic syndrome patients, the initial improvements of several metabolic parameters failed to demonstrate sustained durability at 12 weeks after treatment. An RCT comparing FMT to no intervention in patients with multidrug-resistant organisms failed to demonstrate improved rates of decolonization with treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

**SUPPLEMENTAL INFORMATION**

**Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 5 clinicians associated with 3 physician specialty societies and from 5 clinicians at 2 academic medical centers while this policy was under review in 2014. There was near consensus that fecal transplantation may be considered medically necessary for treating at least some patients with *Clostridioides difficile* infection (CDI). There was also near consensus that fecal microbiota transplant (FMT) is considered investigational for inflammatory bowel disease; moreover, there was a consensus that FMT is considered investigational for conditions other than those previously mentioned. Input was mixed on criteria for selecting patients with CDI for fecal transplantation; in general, the number of FMT recurrences was considered an
important criterion. There was a near consensus among reviewers that there are potential safety concerns associated with FMT, and that these concerns should be studied further before the procedure is offered routinely in clinical practice.

**Practice Guidelines and Position Statements**

**American College of Gastroenterology**
In 2019, the American College of Gastroenterology published guidelines on the management of adults with ulcerative colitis. The guidelines addressed FMT as therapy for induction of remission, as follows:

"Fecal microbiota transplantation (FMT) requires more study and clarification of treatment before use as therapy for UC."

**Infection Diseases Society of America and Society for Healthcare Epidemiology of America**
In 2017, the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America updated clinical practice guidelines for the diagnosis and treatment of CDI in children and adults. Recommendations were summarized as follows:

- "Consider fecal microbiota transplantation for pediatric patients with multiple recurrences of CDI following standard antibiotic treatments. (Weak recommendation, very low quality of evidence)"
- "Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments. (Strong recommendation, moderate quality of evidence)"
- "Potential candidates for FMT include patients with multiple recurrences of CDI who have failed to resolve their infection despite treatment attempts with antibiotic agents targeting CDI. Although there are no data to indicate how many antibiotic treatments should be attempted before referral for FMT, the opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried."

**British Society of Gastroenterology**
In 2019, the British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults made the following recommendation regarding FMT:

- "We suggest that faecal microbiota transplantation (FMT) shows some evidence of benefit in ulcerative colitis and should be used in the context of clinical trials until further high-quality evidence clarifies the potential for benefit and optimal administration protocol (GRADE: weak recommendation, moderate-quality evidence. Agreement: 93.3%)."

**U.S. Preventive Services Task Force Recommendations**
Not applicable.
Medicare National Coverage
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.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 12.

Table 12. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03167398</td>
<td>Fecal Microbiota Transplantation for Eradication of Carbapenem-resistant Enterobacteriaceae Colonization</td>
<td>60</td>
<td>Dec 2019 (completed)</td>
</tr>
<tr>
<td>NCT02255305</td>
<td>Fecal Microbiota Transplantation Versus Standard Medical Therapy for Initial Treatment of Recurrent Clostridium Difficile Infection</td>
<td>60</td>
<td>Dec 2019 (recruiting)</td>
</tr>
<tr>
<td>NCT02592343</td>
<td>Prospective, Open-label Trial to Evaluate Efficacy of Lyophilized Fecal Microbiota Transplantation for Treatment of Recurrent C. Difficile Infection</td>
<td>100</td>
<td>Sept 2020 (completed)</td>
</tr>
<tr>
<td>NCT02269150</td>
<td>A Randomized Controlled Trial of Autologous Fecal Microbiota Transplantation (Auto-FMT) for Prophylaxis of Clostridium Difficile Infection in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation</td>
<td>59*</td>
<td>Oct 2021 (ongoing)</td>
</tr>
<tr>
<td>NCT03562741</td>
<td>Outcomes and Data Collection for Fecal Microbiota Transplantation for the Treatment of Recurrent Clostridium Difficile</td>
<td>500</td>
<td>Jan 2023 (recruiting)</td>
</tr>
<tr>
<td>NCT03804931</td>
<td>Efficacy and Safety of Fecal Microbiota Transplantation for Ulcerative Colitis</td>
<td>120</td>
<td>Dec 2030 (recruiting)</td>
</tr>
<tr>
<td>NCT04521205</td>
<td>A Multicenter Clinical Trial: Efficacy, Safety of Fecal Microbiota Transplantation for Inflammatory Bowel Disease</td>
<td>200</td>
<td>Apr 2024 (recruiting)</td>
</tr>
<tr>
<td>NCT04100291</td>
<td>The Effect of Faecal Microbiota Transplantation in the Treatment of Chronic Pouchitis: A Multicentre, Placebo-controlled, Randomized, Double Blinded Trial</td>
<td>50</td>
<td>Jun 2021 (recruiting)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Reflects actual enrollment.

REFERENCES


Billing Coding/Physician Documentation Information
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

ICD-10 Codes
A04.7 Enterocolitis due to Clostridium difficile
E88.81 Metabolic syndrome
K50-K52 Noninfective enteritis and colitis code range
K59.00-K59.09 Constipation code range
K91.850 Pouchitis

Additional Policy Key Words
N/A

Policy Implementation/Update Information
5/1/15 New Policy. Considered Medically Necessary for patients who meet criteria.
7/1/15 No policy statement changes.
7/1/16 No policy statement changes.
7/1/17 No policy statement changes.
7/1/18 No policy statement changes.
7/1/19 No policy statement changes.
7/1/20 PICO separated for individuals with irritable bowel syndrome. Regulatory Status section updated to include addition of FDA warning for MDRO bacteria in fecal microbiota. Policy statements unchanged.
1/1/21 First policy statement updated with information from 2017 IDSA guidelines for C.diff regarding the number of prior CDIs before FMT is considered (ie, "There have been at least 2 recurrences that are refractory to standard antibiotic treatment").
solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.