LETTER FROM OUR EXECUTIVE DIRECTOR 3
UPDATE FROM OUR CLINICAL PROGRAM DIRECTOR 4
BIANNUAL SAFETY DEBRIEF 5
KEY LESSON LEARNED: IBD 6
ADVERSE EVENT REPORTING 8
ADVERSE EVENT DETAILS 10
Dear Partners,

I am pleased to share OpenBiome’s Biannual Safety and Quality Report for July-December 2017, and hope that you find it instructive and transparent. If you have feedback on the content, please let us know.

As of January 2018, your practice, along with over 1,000 others, has received more than 30,000 FMT preparations for the treatment of recurrent *C. difficile* infection (CDI). In a significant step towards even more widespread impact, last month, the Infectious Disease Society of America and the Society for Healthcare Epidemiology of America jointly released new clinical guidelines for recurrent CDI that call FMT the standard of care.

To facilitate our collective ability to learn from these experiences with FMT, OpenBiome has partnered with the American Gastroenterological Association and the American Gut Project on the FMT National Registry, which aims to follow 4,000 FMT recipients over ten years. The data collected in this study will provide a broad foundation to inform our understanding of the short-term and long-term effects of FMT and support future advancements in patient care.

Since our launch in 2013, we also have partnered with academic investigators on more than 30 clinical trials to explore the interplay between the human microbiome and disease. This year, we are expanding these efforts into a global health context. Building on epidemiological and pre-clinical research, OpenBiome is launching a pilot study in South Africa to evaluate the safety and efficacy of FMT in children with severe acute malnutrition who have failed to respond to standard therapy. We hope to translate discoveries of gut bacteria that can drive promising therapeutic outcomes into scalable new treatments. We are grateful to the Bill & Melinda Gates Foundation and Children’s Relief International for supporting this work.

The evolution of this field in the last five years has been remarkable. We look forward to working alongside you to advance its impact on patients and public health in the years to come.

Sincerely,

Carolyn Edelstein
Executive Director
Dear Clinical Partners,

Thank you for your continued collaboration in enabling safe access to fecal microbiota transplantation (FMT) for patients.

Your participation in the Material Tracking Log and Follow-Up Form Program has been invaluable as we strive to ensure the highest levels of safety across our network. We rely on the information you provide to continuously monitor efficacy and patient safety throughout our network. Please continue to report any suspected adverse events to us at www.OpenBiome.org/Adverse-Events.

In the second half of 2017, 18 serious adverse events were reported to OpenBiome: 15 were determined to be unrelated to FMT, and three were identified as possibly related to FMT. No reported AEs were determined to be definitely related to FMT material.

Additional information on these reports can be found on page 8.

We enjoyed seeing presentations from several of you at the Clinician’s Guide to FMT Workshop, held as part of the 2018 Crohn’s & Colitis Congress in January, and continue to be inspired by the commitment and innovation shown by the clinical providers who drive the practice of FMT forward every day.

We were also pleased to see the new guidelines for treatment of C. difficile from the Infectious Diseases Society of America (IDSA) include FMT as a treatment for recurrent C. difficile for the first time. As the adoption of FMT treatment continues to grow, thanks to the tireless efforts of clinicians and patient advocates, we are encouraged by the inclusion of FMT in these guidelines. This will open the door to FMT for even more patients suffering from recurrent C. difficile.

I look forward to meeting many of you at Digestive Disease Week in June, and I am grateful for your continued collaboration as we expand safe access to FMT. We appreciate your feedback and welcome any specific issues you would like to see addressed in future editions of this report.

Dr. Majdi Osman, MD MPH  
Clinical Program Director
From June 15, 2017 through December 15, 2017, 18 adverse events were reported to OpenBiome by members of our clinical network. Below, we have aggregated patient characteristics from reported adverse events and lessons learned from the subsequent investigations.

**Patient characteristics in suspected adverse events.** Half of the patients involved in adverse events were reported as having severe or severe-complicated CDI (50.0%, n=9). The most common treatment modalities were liquid preparations delivered via the lower gastrointestinal tract (61.1%, n=11) and upper gastrointestinal tract (33.3%, n=6). There were no reports of adverse events involving FMT capsules.

Reported adverse events are graded according to severity by NIH grading criteria (Figure 1).

**Adverse Event (AE) NIH Relatedness.** Based on information gathered through in-depth collaborative investigations with reporting partners, all cases were classified according to NIH Relatedness definitions. Twenty-five of the reported AEs (83.3%) were determined to be not related to the FMT material and the remaining 3 AEs (16.7%) were identified as possibly related to the FMT material. **No reported AEs were determined to be definitely related to FMT material.**

1. Disease Adverse Event Grading Scale, National Institutes of Health

   **Grade 1.** Mild: Symptoms causing no or minimal interference with usual social & functional activities
   **Grade 2.** Moderate: Symptoms causing greater than minimal interference with usual social & functional activities
   **Grade 3.** Severe: Symptoms causing inability to perform usual social & functional activities
   **Grade 4.** Potentially Life Threatening: Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, or persistent disability
   **Grade 5.** Death

2. Definitions of Relatedness, National Institutes of Health

   **Not Related:** The adverse event is clearly not related to the investigational agent/procedure. - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.
   
   **Possibly Related:** An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
   
   **Definitely Related:** The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject’s clinical state.

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**Fig. 1: Adverse Events by NIH Severity Grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Mild)</td>
<td>0</td>
</tr>
<tr>
<td>2 (Moderate)</td>
<td>0</td>
</tr>
<tr>
<td>3 (Severe)</td>
<td>6</td>
</tr>
<tr>
<td>4 (Pot. Life-Threat)</td>
<td>6</td>
</tr>
<tr>
<td>5 (Death)</td>
<td>6</td>
</tr>
</tbody>
</table>

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Patients with both *C. difficile* infection (CDI) and inflammatory bowel disease (IBD) can be challenging to treat. At this point, the evidence on the interplay between CDI, IBD and FMT remains unclear. Below is a summary of the current published literature, highlighting the potential risks and the potential benefits of treating IBD patients with FMT. We continue to advise that all patients with IBD should be counselled on the potential risks, benefits and alternatives to FMT through appropriate informed consent process.

In patients with both CDI and IBD, worsening IBD disease activity is a potential complication of FMT treatment. In a recent systematic review and meta-analysis of 29 studies with 514 patients, up to 15% of patients with both CDI and IBD experienced a flare post-FMT (Qazi et al., 2017). In a study of 272 patients who underwent FMT for CDI, cure rates were observed to be lower in patients with comorbid IBD than patients without IBD (74.4% vs 92.1%; *p* = .0018) (Khoruts et al., 2016). Confounding this potential relationship is that patients with IBD are at an increased risk of flare during CDI, which makes it difficult to assess the direct effect of FMT on IBD disease activity.

In patients with IBD without CDI, there is a growing body of evidence that FMT may ameliorate the symptoms of IBD and reduce the frequency of flares. Recent findings from the landmark FOCUS study revealed the potential benefits of FMT in ulcerative colitis in a large, double-blind, randomized controlled trial comparing FMT against a placebo (Paramsothy et al., 2016). Similar findings have been replicated in a further recent randomized controlled trial (Costello et al., 2017).

It is important to note that, while the FDA allows FMT for the treatment of CDI with comorbid IBD under enforcement discretion, the FDA does not allow FMT for the treatment of IBD alone, and that patients participating in the latter two studies were enrolled in IBD clinical trials.

In summary, the evidence is not yet conclusive regarding the potential effects of FMT on IBD, particularly in the context of CDI. FMT has been shown to potentially decrease cure rates and may be associated with post-treatment flares in IBD patients with CDI; it has also been shown to reduce flares and ameliorate symptoms of IBD patients without CDI. Patients should receive informed consent before proceeding with treatment.
REFERENCES


Common, mild adverse reactions after FMT delivery:

Mild, self-limiting symptoms may occur after FMT and should be clearly discussed with patients during informed consent. Based on the peer-reviewed literature, potential expected non-serious adverse reactions that can be anticipated after FMT are:

- Transient diarrhea
- Transient abdominal cramps or discomfort
- Nausea
- Constipation
- Excess flatulence

In addition to the above, mild fever, bloating, vomiting, and borborygmus have been reported to occur after FMT. Expected mild adverse reactions do not require reporting to OpenBiome.

Managing treatment failure:

CDI recurrence or non-response have been known to occur in approximately 10-20% of patients post FMT for reasons unrelated to the FMT material. In events where CDI recurrence or non-response is suspected (e.g. development of or continued diarrhea, abdominal pain, etc.), an infectious disease work-up should be conducted to rule out other infectious etiologies. Non-infectious etiologies should also be considered (e.g. post-infectious IBS). Cases where CDI recurrence or non-response has been confirmed do not require reporting to OpenBiome.

Serious adverse events that warrant reporting:

While there have not been any definitely related serious adverse events attributable to FMT material, should a serious adverse event (SAE) occur within a reasonable timeframe post-FMT where relatedness of the FMT material cannot be definitively ruled out, these SAEs should be reported to OpenBiome. Examples of such SAEs include:

- Post-FMT new onset of infectious diarrhea
- Post-FMT new onset of sepsis
- Allergy or anaphylaxis

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There is a theoretical risk of developing disease that may be related to donor gut microbiota. These include obesity, metabolic syndrome, cardiovascular disease, autoimmune conditions, allergic/atopic disorders, neurologic disorders, psychiatric conditions and malignancy. People with these and similar conditions are excluded from donating stool to OpenBiome. However, if an FMT recipient appears to be experiencing a new onset of any of these diseases and FMT is suspected, this should be reported.

In addition to the above, any SAEs as defined by the FDA (21 CFR 312.32(c)(1)(i)) where there is uncertainty in the relationship between the event and the FMT, must be reported to OpenBiome.

Adverse events should be reported to OpenBiome through the online portal (www.openbiome.org/adverse-events). Clinicians may contact the Safety Team directly (617-575-2201 ext. 9) to discuss whether an SAE requires reporting.

**Clinical Vignette:** The following vignette is an illustrative example of SAEs that must be reported to OpenBiome to safeguard patient safety.

<table>
<thead>
<tr>
<th>Background: 57 y/o male with history of Ulcerative colitis, diabetes mellitus, pancreatic insufficiency</th>
<th>Summary: A 57-year-old male patient with recurrent CDI not responsive to standard therapy (Modified Horn Index 2) underwent FMT via colonoscopy without complication. At the time of FMT, the patient was noticed to have moderate pan-colitis in the setting of recurrent CDI. The patient tolerated the procedure well and was discharged home in a stable condition. Patient was prescribed mesalamine following discharge, but he continued to experience diarrhea and eventually presented to the emergency department with low-grade fever on Day 3 post-FMT. Abdominal examination was benign. Labs showed persistent hypokalemia (2.4 mmol/L), hypocalcemia (7.1 mmol/L), leukocytosis (16.5 x 10⁹ per L), along with anemia (Hb: 9.7g/dL). The patient was admitted and infectious workup returned negative for <em>Clostridium difficile</em>. Endoscopic evaluation was suggestive of moderate to severe colitis. Prevailing diagnosis was thought to be an IBD flare post-FMT. The patient responded to IV and oral steroid therapy with resolution of inflammatory symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event: IBD Flare</td>
<td><strong>Severity:</strong> Grade 3 (Severe)</td>
</tr>
<tr>
<td><strong>Relatedness:</strong> Possibly related</td>
<td></td>
</tr>
</tbody>
</table>
All adverse events reported to OpenBiome that were possibly related to FMT and investigated between July and December 2017 are summarized in the table below. Clinicians who are interested in learning more about specific adverse events reported to OpenBiome are welcome to request a copy of the detailed case narratives by contacting safety@openbiome.org.

<table>
<thead>
<tr>
<th>Summary</th>
<th>CDI type</th>
<th>Severity (NIH grade)</th>
<th>Relatedness (NIH definition)</th>
<th>Background</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em> bacteremia</td>
<td>Recurrent CDI, Severe</td>
<td>Grade 4, Potentially Life-Threatening</td>
<td>Possibly related</td>
<td>98F with history of hypertension, leukocytosis</td>
</tr>
<tr>
<td>IBD Flare</td>
<td>Recurrent CDI, Mild-Moderate</td>
<td>Grade 3, Severe</td>
<td>Possibly related</td>
<td>57M with history of Ulcerative colitis, diabetes mellitus, pancreatic insufficiency</td>
</tr>
<tr>
<td>IBD Flare</td>
<td>Recurrent CDI, Mild-Moderate</td>
<td>Grade 4, Potentially Life-Threatening</td>
<td>Possibly related</td>
<td>35M with history of Primary sclerosing cholangitis, Crohn’s disease</td>
</tr>
</tbody>
</table>