Dear Partners,

I am pleased to share OpenBiome’s Biannual Safety and Quality Report for January-June 2017.

As of June 21, your FMT practice, along with those at 900 other medical centers that have partnered with OpenBiome, have accepted more than 25,000 treatments. We are proud to be working with you to reach C. difficile patients who have few treatment alternatives.

As we work to overcome the logistical barriers to FMT, we continue to rely on your input in shaping our clinical education and safety program. FMT has entered standard clinical practice, with five randomized controlled trials showing the efficacy and short-term safety profile of the treatment. It is our goal to continue to evaluate and improve upon this treatment, in partnership with you.

To that end, we were glad to see many of you again at Digestive Disease Week in May. There, OpenBiome researchers shared findings of interest to this community, including a poster of distinction showing that pediatric C. difficile patients have more limited access to FMT than the adult population. Budree and colleagues found that 72% of the U.S. population lives within a 4-hour drive of a pediatric FMT provider, while previous research has shown that 99% of adult patients live within 4 hours of an FMT facility.

Dr. Budree also presented findings on donor-specific factors that theoretically could affect FMT efficacy for recurrent CDI: donor metabolomics, diet, stool consistency, and laboratory processing time. Budree and his colleagues found that none significantly changed patient outcomes. The researchers suggested that other variables such as patient-specific factors may cause differences in cure rates for FMT in recurrent CDI.

We look forward to sharing future findings with you as we collaborate to advance clinical care and support the emergence of the microbiome’s role in medicine.

Sincerely,

James Burgess
Executive Director
Dear Physicians and Allied Health Professionals,

Thank you for your continued collaboration in enabling safe access to fecal microbiota transplantation (FMT) for patients. It has been an honor working with you all, and our collective progress is reflected in the significant milestone of shipping our 25,000th treatment.

Since our last report, I am pleased to inform you that we have had no adverse events related to FMT. However, we continue to require you to report suspected adverse events to us at openbiome.org/adverse-events.

In the first half of 2017, 27 serious adverse events were reported to OpenBiome; 25 were determined to be not related to FMT, and two were identified as possibly related to FMT. No reported AEs were determined to be definitely related to FMT material. You may read more about these reports on page 7.

A key pillar of our work at OpenBiome is on clinical education and quality improvement in FMT. Over the coming months, we will be rolling out a series of educational tools centered on the “5D framework” to help clinicians take a straightforward, evidence-based approach to FMT. This approach will navigate how to decide if the CDI patient is appropriate for FMT, select and screen stool donors, identify the ideal delivery modality, discuss the risks and benefits of FMT with your patient, and practical considerations on discharge and follow-up after FMT.

You may preview this approach in Allegretti et al (2017) “The 5D framework: a clinical primer for fecal microbiota transplantation to treat Clostridium difficile infection”, in Gastrointestinal Endoscopy and view our summary on page 6 of this report.

As always, we greatly appreciate your feedback. If there are specific areas you would like to see addressed, please do not hesitate to reach out to me, and thank you again for your continued collaboration.

Dr Majdi Osman MD MPH
Clinical Program Director, OpenBiome
From January through June 15, 2017, 27 adverse events were reported to OpenBiome by members of our clinical network. Below, we have aggregated patient characteristics in suspected adverse events and lessons learned from the subsequent investigations.

**Patient characteristics in suspected adverse events.** Patients involved in adverse events predominantly had a Modified Horn’s Index 3 or higher (66.7%, n=18). Additionally, 55.6% (n=15) of recipients were reported as having severe or severe-complicated CDI. Treatment modalities were liquid infusions delivered via the lower gastrointestinal tract (81.5%, n=22) and upper gastrointestinal tract (18.5%, n=5).

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

**Adverse Event 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 (92.6%) were determined to be not related and the remaining 2 AEs (7.4%) were identified as possibly related to FMT. No reported AEs were determined to be definitely related to FMT material.

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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.
In June, Dr. Jessica Allegretti, MD, MPH, Director of the Fecal Transplant Program at Brigham & Women’s Hospital, and Dr. Zain Kassam, OpenBiome, co-authored a clinical primer with colleagues titled “The 5D framework: a clinical primer for fecal microbiota transplantation to treat Clostridium difficile infection” published in Gastrointestinal Endoscopy. The primer covers the decision process for evaluating your patient’s suitability for FMT, determining the appropriate donor, key points for an informed consent discussion, choosing the optimal delivery modality and best practice for discharge.

**5Ds of FMT for C. diff**

**1. Decision**
Two step testing (PCR then GDH) to diagnose active C.diff infection.

**2. Donor**
Universal donors often undergo more robust screening than is feasible when using patient-identified donors. In some cases, a patient-identified or “directed donor” approach should be considered.

**3. Discussion**
The patient should give informed consent and be trained on how to prepare for FMT.

**4. Delivery**
FMT may be infused via the upper GI tract, lower GI tract, or delivered with pills.

**5. Discharge**
Patients should receive training on caring for themselves after FMT.

Follow-Up at 8 weeks:
Evaluate for clinical symptoms recurrent C. diff infection, post infectious irritable bowel syndrome, and adverse events.

Click here to read more.
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 review 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.

CDI Recurrence / Non-Response:

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 evaluated for (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 and be suspected to related to FMT material, 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. 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 using the online reporting portal (openbiome.org/adverse-events). Alternatively, clinicians may contact the Safety Team directly (617-575-2201 ext. 9) to discuss whether an SAE requires reporting.

Clinical Vignette: Serious Adverse Event (bacteremia of unknown origin)
The following vignette is an illustrative example of an SAE that must be reported to OpenBiome to safeguard patient safety.

<table>
<thead>
<tr>
<th>Background:</th>
<th>27 y/o male with history of sickle cell disease, splenectomy, recurrent bacteremia, and recent stem cell transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary:</td>
<td>Approximately 24 hours post FMT, the patient presented with high grade fever and blood culture positive for non-Shiga producing Escherichia coli. There were no clear signs, history or laboratory findings suggestive of a source. Specifically, urine, stool and line sites returned negative on infectious disease work-up. The patient was admitted to the ICU and treated with IV antibiotics. The patient’s symptoms responded promptly to therapy and he was discharged 14 days post-admission. The patient’s baseline immunosuppression on a background of recurrent polymicrobial sepsis (occurring on a monthly basis) most likely increased the patient’s risk for a coincidental episode of bacteremia post-FMT. In all cases, including this reported event, no infectious source was identified. WBC count prior to the FMT was noted to be elevated at 17.2 x10⁹/L. Although this case is unlikely to be related to FMT, no definitive source of infection was identified and therefore FMT attribution cannot be definitively determined. The case was therefore categorized as possibly related to FMT.</td>
</tr>
<tr>
<td>Adverse event:</td>
<td>Escherichia coli bacteremia</td>
</tr>
<tr>
<td>Severity:</td>
<td>Grade 4 (Potentially Life-Threatening)</td>
</tr>
<tr>
<td>Relatedness:</td>
<td>Possibly related</td>
</tr>
</tbody>
</table>
All adverse events reported to OpenBiome that were possibly related to FMT and investigated between January and June 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>Escherichia coli bacteremia</td>
<td>Recurrent CDI, Severe- Complicated</td>
<td>Grade 4. Potentially Life-Threatening</td>
<td>Possibly related</td>
<td>27M, sickle cell disease, splenectomy, recurrent bacteremia, CMV+, post-stem cell transplant</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Recurrent CDI, Mild-Moderate</td>
<td>Grade 3. Severe</td>
<td>Possibly related</td>
<td>75F, Crohn’s disease</td>
</tr>
</tbody>
</table>