OpenBiome Quality Metrics

Donor Assessment | Stool Collection & Production Controls | Quality Assurance

Purpose
This section summarizes the assays and process controls that OpenBiome has developed to ensure consistent quality and minimize the risk of adverse events.

Documentation
Copies of relevant de-identified screening reports are included in each shipment for all donors that have contributed material to the units being shipped. This documentation is provided to enable OpenBiome's clinical partners to review and interpret these results directly and make their own informed medical decision about the suitability of this material for use in their medical practice.

Disclaimer
Although OpenBiome has designed a rigorous screening regimen, there are risks associated with the use of these materials, including, but not limited to the potential for the presence of infectious agents, risk factors for non-infectious diseases or pathogens that were not detected by the assays employed. The treating physician should weigh the risks and benefits for each patient to determine the suitability of fecal microbiota transplantation (FMT).

Finch Therapeutics
As of March 1, 2017, OpenBiome has licensed its quality systems to Finch Therapeutics to carry out biomanufacturing of FMT preparations. As the manufacturer, Finch Therapeutics is responsible for implementing certain aspects of OpenBiome's Quality & Safety Program.

A. Clinical Assessment
Prior to enrollment, donors (age 18-50), receive informed consent with oversight from the New England Institutional Review Board (IRB). Donors are assessed by a registered nurse and/or physician with final review by an internal medicine specialist to determine if they meet the following exclusion criteria:

1. **Infectious risk factors:**
    a. Known HIV or viral hepatitis exposures
    b. High risk sexual behaviors
    c. Use of illicit drugs
    d. Tattoo or body piercing within previous 6 months
    e. Incarceration or history of incarceration
    f. Known history of tropical infection or current communicable diseases

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g. Other personal infectious disease risk factors including Creutzfeldt-Jakob disease (CJD)
h. Travel history to endemic regions with a high risk acquiring infectious pathogens
i. Risk factors for multi-drug resistant organisms (MDROs) including work in clinical environment or long-term care facility

2. Potentially microbiome-mediated conditions:

a. Gastrointestinal conditions (e.g., history of IBD, IBS, chronic constipation, chronic diarrhea, Celiac disease)
b. Atopic conditions (e.g., asthma, atopic dermatitis, eosinophilic disorders of the gastrointestinal tract)
c. Autoimmune conditions
d. Chronic pain syndromes
e. Metabolic conditions (i.e. clinician assessment of BMI and waist circumference)
f. Neurological conditions
g. Psychiatric conditions
h. Malignancy history
i. Surgeries / Other medical history
j. Current symptoms
k. Medications including antibiotics, antifungals, antivirals, and immunosuppressants
l. Diet
m. Family history (e.g., family history of IBD, colon cancer)

B. Laboratory Screening

Prospective donors that do not meet any of the exclusion criteria outlined above are then subjected to a battery of serological, stool-based, and nasal swab assays to determine whether infectious pathogens are present. All tests are outsourced to third-party Clinical Laboratory Improvement Amendments (CLIA) certified testing facilities. As a condition for participation in this program, donors are required to submit written authorization for the disclosure of the results of these tests to Finch Therapeutics, in compliance with the Health Insurance Portability and Accountability Act (HIPAA). Finch redacts all personal identifying information from each report and shares copies of de-identified diagnostic reports with OpenBiome's clinical partners. Documentation is provided for the battery of tests prior to enrollment of a donor and for tests performed at the end of the collection period. Abnormal infectious pathogen tests are treated as exclusion criteria for all materials:

1. Serologic testing:

a. Complete blood count with differential
b. Hepatic function panel (AST, ALT, ALP, bilirubin, albumin)
c. HIV-1/2 antigen and antibodies, Fourth Generation
d. Hepatitis A (IgM)
e. Hepatitis B panel, (IgM anti-HBc, anti-HBc; HBsAg)
f. Hepatitis C (HCV antibody)

g. *Treponema pallidum* (Cascade with reflex to RPR)
h. HTLV I and II, antibody
i. Strongyloides IgG, antibody

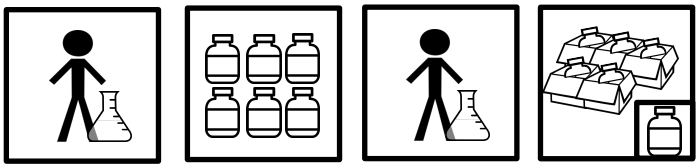
2. **Stool testing:**
   a. *Clostridium difficile* toxin B, PCR
   b. Culture-based assays for common enteric pathogens (including *Salmonella*, *Shigella*, *Campylobacter, Vibrio)*
   c. Shiga toxin EIA with reflex to E.coli 0157 culture
   d. *Helicobacter pylori,* EIA
   e. Ova and parasites
   f. *Giardia lamblia,* EIA
   g. *Cryptosporidium,* EIA
   h. *Cyclospora and Isospora,* Microscopic exam
   i. *Microsporidia*, Microscopic exam
   j. Rotavirus, EIA
   k. Norovirus, Real-time PCR
   l. Adenovirus, EIA
   m. Vancomycin-Resistant Enterooccus (VRE), culture-based assay
   n. Extended spectrum beta-lactamase (ESBL), culture based assay
   o. Carbapenemase producing gram-negative rods (CRE), culture based assay
3. **Nasal Swab Culture:**
   a. Methicillin-resistant Staphylococcus aureus (MRSA), culture based assay

C. Continuous Requalification System

Prospective donors that meet the clinical and laboratory inclusion criteria described above are enrolled as active donors. Once enrolled, donors are carefully assessed for changes in health status. Our continuous requalification system ensures that material is not released for clinical use until donors have passed our rigorous battery of clinical and laboratory evaluations both before and after the material was produced. Our continuous requalification system includes the following features:

1. **Collection period:** Qualified Donors that meet the above criteria are enrolled to provide material for FMT. Donor material is collected for up to 60 days following the initial screening. During this collection period donors must not violate any of the risk factors identified in Part A.

2. **Quarantine and dual testing:** All material collected in the collection period is placed in quarantine until the donor has passed a second battery of clinical, serological and stool assessments, as described in Part A and B. Material is only released for clinical use after the donor has successfully passed dual testing, specifically two complete clinical assessments and two full sets of the assays described above both before and after the collection period. Dual testing helps mitigate the risk of false negative intrinsic to some laboratory tests and ensures that the health status of a donor hasn't changed after initial testing.



1. Qualified donor passes clinical, serol-ogical & stool assessment

2. Stool is collected over 60 days & quarantined

3. Donor re-qualifies by passing clinical, stool & serological assessment

4. Quarantined stool released for clinical use. Stool collected <21 days prior to donor's re-qualification stays in quarantine.

3. **Seroconversion window:** Testing of individual samples also carries with it the possibility of false negatives from recent infection falling within an infective seroconversion window. Accordingly, a 21-day seroconversion delay is employed before release of any material. Consequently, material in the final 21 days of a collection window is not released until a third screening is performed outside the 21-day seroconversion window.
4. **Safety aliquot:** Multiple samples of all material are preserved for at least 24 months. If there is a suspected adverse event, the exact material that was used in the recipient may be assessed for pathology.
5. **Quality Assurance Monitoring**: In contrast to directed donor approaches, de-identified quality assurance data on efficacy and safety is collected from other patients treated with each donor. As a result, in addition to the intensive laboratory and clinical assessments described above, many of our donors have previously provided material that has already been safely and effectively used in dozens, or even hundreds of other patients. This direct clinical-track record mitigates the risk of future FMTs from these experienced donors.

D. Continuous Donor Health Monitoring

In between screens conducted in our continuous requalification system, donors are under active medical supervision as described below:

1. **Quality controls at the time of collection for <u>each</u> donation**:
    a. Physician-trained technician performs in-person, general health inspection upon sample check-in. If there are any concerns or signs of illness, the material is destroyed and the donor is suspended with a comprehensive physician-led clinical assessment to determine donor eligibility.
    b. Donors are required to complete health status update outlining any behavioral changes, illness or exclusion criteria risk factors during sample

check-in process. Any clinical concern triggers a comprehensive physician-led clinical assessment to determine donor eligibility.

c. The sample is assessed by a physician-trained technician for 2 factors:
    i. Stool Pathology (melena, hematochezia, mucus). Any sample with concerns for pathology is documented and discarded, triggering a comprehensive physician-led clinical assessment to determine donor eligibility.
    ii. Stool Quality (Bristol Stool Score 3-5). All Bristol Stool Score 1-2 samples (constipation) and Bristol Stool Score 6-7 (diarrhea) are documented and discarded, triggering a comprehensive physician-led clinical assessment to determine donor eligibility.

2. Randomized Quality Assurance Assessment

a. Donor Health Check: All donors undergo periodic, random health checks by a registered nurse and/or physician supervised by an internal medicine specialist. During the health check, a clinician performs a brief clinical assessment and measures vital signs including BMI, waist circumference, blood pressure, and temperature.

3. Clinical Monitoring

a. 24/7 On-Call Access: All donors have on-call access to a registered nurse or physician in the event of a health concern or question.

b. Defined Illness Protocols: In the event that the donor experiences any abnormal symptoms, including fever or a change in bowel habit, donors are instructed to notify Finch Therapeutics immediately. Donors discuss their symptoms with a clinician and are directed to their primary care provider (PCP), if needed. If the clinician determines that the donor's symptoms could impact the health of a recipient, the donor is temporarily suspended from participation awaiting examination of the underlying symptoms by clinical assessment and/or diagnostic tests. In the event that a relevant diagnosis is confirmed, the donor is retired from the program at the discretion of the Finch Chief Medical Officer and/or Finch Clinical Advisory Board (CAB), which includes thought leaders in infectious diseases, medical microbiology and gastroenterology. All material collected from an excluded donor in the preceding collection period is destroyed. In the event of transient or non-concerning symptom, donors will be re-enrolled when symptoms are resolved and at the discretion of the Finch Chief Medical Officer and/or Finch CAB.

4. Incidental Findings:

a. In the event of minor, non-contributory, incidental finding (e.g. CBC, liver function panel), a physician-led focused clinical assessment will occur. The physician will determine ongoing eligibility, and provide a summary and rationale in the

documentation sent to health care institutions to help a patient's primary physician evaluate clinical suitability.

E. Production and Process Controls

Within Finch's processing facility, technicians follow a carefully validated set of standard operating procedures to ensure consistent quality production. Below we have summarized the basic workflow that is used to register, process and track samples during production:

6. The donor deposits stool in a commode, seals the lid, and places the collection container in one re-sealable LDPE plastic bag (Ri-Pac 2GN or similar) as secondary containment. Donors receive training to prevent contamination during collection.
7. The sealed sample collection container is transferred from the donor to a qualified technician.
8. The mass of the sample is measured, subtracting the tare weight of the collection container.
9. Samples are transferred to a UV-sterilized biosafety cabinet cleaned with a sporicidal agent dedicated for sample processing and isolated from any other processes or materials within Finch's facility.
10. Within the biosafety cabinet, the stool is transferred to a sterile, disposable filter bag. The filter bag fits around the collection commode entirely, so there is no risk of material escaping during this transfer process. All stool material will be added to the same side of the membrane in the filter bag.
11. Sterile dilutant consisting of 12.5% glycerol and a normal saline buffer (0.90% w/v NaCl in water) is added to the filter bag. The volume of buffer added is normalized to the mass of the sample.
12. The sample solution sealed inside the filter bag is then introduced to a homogenizer blender for 120 seconds to suspend the bacterial communities in the aqueous phase buffer. Fibrous material is contained on one side of the bag, while a liquid suspension of the bacterial community is collected on the other side of the 330 micron filter.
13. Samples are then aliquoted into sterile bottles using sterile, disposable serological pipettes.
14. The bottles are capped and frozen immediately at -80°C. Caps are sealed with tamper-evident, perforated PVC shrink bands to ensure samples have an additional level of containment and are not contaminated or tampered with during storage and distribution.
15. Samples are delivered to clinicians on dry ice, in double-containment vessels, with temperature indicators to ensure that samples have not thawed during transportation.
16. Each sample is labeled with a unique barcode enabling full batch traceability.