



OPENBIOME

Clinical Considerations for Donor Selection

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Abstract

Evaluating the health of stool donors providing Fecal Microbiota Transplantation (FMT) material is a crucial and dynamic aspect of stool banking. Donor selection criteria may vary depending on multiple factors such as geography and patient population, and is continually being updated to reflect the latest understanding of FMT and the microbiome. This paper reviews clinical considerations underlying donor selection using OpenBiome’s screening criteria as an example.

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Introduction

Stool donor selection follows two basic principles:

1. **Donor selection should aim to limit the risk associated with Fecal Microbiota Transplantation (FMT) without unduly restricting access to the procedure.** This objective follows the risk management doctrine of ALARP (“as low as reasonably practical”) or ALARA (“as low as reasonably achievable”), which is used by blood banks. ALARP and ALARA recognize that, although nearly infinite time and resources could be spent in reducing risk to near zero, such efforts may not benefit patients if FMT material becomes inaccessible due to cost or availability. In balancing the potential risks and benefits of FMT, OpenBiome has implemented a donor selection process that qualifies three percent of prospective stool donors.¹
2. **Donor screening criteria should be continuously evaluated and updated to reflect the most up-to-date understanding of the potential risks of FMT and, more generally, the microbiome.** The short-term safety profile of FMT suggests a low risk to the general patient population but new long-term data, data regarding specific patient populations, or identification of new infectious and noninfectious safety risks may require updates to screening protocols. Furthermore, as technology for screening enteropathogens is improved (e.g. increasing access to novel culture-independent methods) it is important for donor screening methods to be reappraised regularly.

Using these two principles, stool banks can design their own donor selection criteria that will include a basic threshold for safety common to all banks as well as more specific criteria applicable to the stool bank's operating context.

Note: This paper focuses on designing donor selection criteria. A related paper titled “The Logistics of Donor Screening” covers practical considerations of implementing screens such as frequency of screening and how to optimally guide prospective donors through multiple rounds of health evaluation.

Common Selection Criteria

Although there are no formally standardized, comprehensive donor screening criteria issued by regulators (as with blood banking and tissue products), a growing consensus has emerged in recent years around a core set of donor evaluation measures that have been recommended or required by the following sources:

- [Recommendations](#) from the FMT Workgroup published in 2011.²
- [Joint recommendations](#) from the Infectious Diseases Society of America (IDSA), American Society for Gastrointestinal Endoscopy (ASGE), North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), American Gastroenterological Association (AGA), and American College of Gastroenterology (ACG). These recommendations were written as a letter in 2013 from the presidents of these organizations to the United States Food and Drug Administration (FDA).
- An [international consensus conference](#) on stool banking in 2019.³
- [Safety alerts](#) from the FDA

A summary of consensus donor evaluation criteria is summarized below. These criteria synthesize recommendations from these sources as well as standardized screening recommendations used in blood banking . Donor evaluation relies on questionnaires to identify risk of indications for which there are no laboratory tests and using appropriate diagnostics for indications that can be tested for.

Infectious Disease

Donors should be asked, via questionnaire or an in-person clinical interview, to disclose known history or risk factors for the following infectious agents:

- Known HIV, Hepatitis B or C infections or exposure to those viruses within the previous 12 months
- High-risk sexual behaviors or use of illicit drugs
- Tattoo or body piercing within the past 6 months
- Incarceration or history of incarceration
- Known communicable disease
- Risk factors for variant Creutzfeldt-Jakob disease
- Travel history, especially within the past 6 months, to endemic regions with a high risk of acquiring infectious pathogens
- Risk factors for multi-drug resistant organisms (MDROs) including work in clinical environment or long-term care facility; persons who have recently been hospitalized or discharged from long term care facilities; persons who regularly attend outpatient medical or surgical clinics; persons who have recently engaged in medical tourism

Donors should be screened for following pathogens and organisms by blood testing

- Hepatitis A, B, C, and E
- HIV-1 and HIV-2
- Strongyloides IgG

Donors should be screened for the following pathogens and organisms by stool testing

- *Clostridioides difficile*
- Common bacterial enteropathogens: *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., *Plesiomonas shigelloides*, *Vibrio* spp.
- Diarrheagenic *E. coli* (e.g. Shiga toxin-producing *E. coli*)
- Multi-Drug Resistant Organisms: Vancomycin-Resistant Enterococci (VRE), Extended Spectrum Beta-Lactamase producing Enterobacteriaceae (ESBL), Carbapenem-resistant Enterobacteriaceae (CRE)
- Viral enteropathogens: Norovirus, Rotavirus, Adenovirus, Astrovirus, Sapovirus
- Diarrheagenic parasites: *Giardia lamblia*, *Cryptosporidium* spp, Isospora and Microsporidia

Methods of detection: An important consideration when developing donor screening is to consider the methods of detection for each of target organisms. Detection methods should consider sensitivity and specificity, cost, ease of administration and is acceptable to donors, regulators, patients and practitioners.

Culture-based methods may present the gold-standard for some organisms, but for a donor screening program a high sensitivity assay may be more desirable (i.e. a test has a higher ability to designate an individual with an infection as positive). For further reading on this topic we recommend reading this paper: Zellmer C, Sater MRA, Huntley MH, Osman M, Olesen SW, Ramakrishna B. [Shiga Toxin-Producing Escherichia coli Transmission via Fecal Microbiota Transplant](#). Clin Infect Dis. 2021 Jun 1;72(11):e876-e880. doi: 10.1093/cid/ciaa1486. PMID: 33159210.

Incidental findings: Lastly, depending on the method of screening, it is possible that incidental results may be found. An example of this is detection of *Blastocystis hominis* on microscopy for ova and parasites (O&P). Microscopy for O&P is commonly used to assess for parasites in donor screening programs. *B. hominis* is commonly carried in healthy individuals and the role of *B. hominis* in causing diarrhea is poorly understood. Nevertheless, even though donor screening programs often do not explicitly list *B. hominis* as an exclusion criteria most stool banks considered it an exclusion if detected.

Therefore, it is important to consider *a priori*, how incidental findings from each of the assays will be handled.

Disorders potentially associated with the microbiome

Donors should be asked, via questionnaire or an in-person clinical interview, to disclose known history or risk factors for the following indications:

- Recent gastrointestinal symptoms such as diarrhea or hematochezia
- Chronic gastrointestinal disease
- Systemic autoimmune disorders

- Cancer or family history of cancer
- Neurological or neurodegenerative disorders
- Psychiatric or neurodevelopmental conditions
- Obesity (body mass index over 30) or metabolic syndrome/diabetes

General Health and Medication

Donors should be evaluated, via questionnaire or an in-person clinical interview, for general health factors and medication use.

- Metabolic conditions (clinician assessment of BMI and waist circumference)
- Medications including antimicrobial drugs and immunosuppressants
- Chronic use of medications (e.g. proton pump inhibitors)

Donors should be screened for following health markers by blood testing:

- Complete blood count with differential
- Hepatic function panel (AST, ALT, ALP, bilirubin, albumin)

Changes to Health

Before each stool donation, donors should communicate any changes or signs of potential change to their health with the stool bank's donor and/or clinical staff.

Changes in health include:

- New gastrointestinal symptoms
- New signs of infections such as fever or swollen lymph nodes
- New use of medications
- New travel
- New sexual partners

SARS-CoV-2

Early in the COVID-19 pandemic it was observed that viable SARS-CoV-2 could be shed in stool. There have been no reported cases of fecal-oral transmission of SARS-CoV-2 causing infection and it is not recognized as mode of transmission. However, given the potential for shedding of SARS-CoV-2 in stool the scientific community recognized early on that FMT donor screening should be adapted to mitigate any potential risk of transmission.

On April 9, 2020, the FDA released a [safety alert](#) outlining required safety measures to mitigate the risk of transmission of SARS-CoV-2 via FMT material.

FMT preparations manufactured before December 1, 2019, are not eligible for patient use until additional testing procedures and changes to the informed consent process are implemented as described below:

1. Assess, via questionnaire and clinical interview, whether the donor has been diagnosed with laboratory-confirmed SARS-CoV-2 infection, experienced symptoms of COVID-19 (e.g., fever, cough, shortness of breath) not explained by another diagnosis, or was exposed to a suspected or confirmed case of COVID-19 or SARS-CoV-2 infection.
 - a. If the donor reports any instances of suspected or confirmed SARS-CoV-2 infection or exposure, they will be excluded from further donations and any FMT product manufactured from their stool beginning 4 weeks prior to the suspected or confirmed SARS-CoV-2 will be excluded from clinical use.
2. Directly test stool donations or stool donors for SARS-CoV-2 virus or RNA
 - a. Testing could include periodic SARS-CoV-2 screening by nasopharyngeal swab every 14 days or directly testing each donated stool sample for the presence of viral DNA.
 - b. If SARS-CoV-2 is detected, the donor will be excluded from further donations and any FMT product manufactured from their stool beginning 4 weeks prior to first positive test will be excluded from clinical use.
3. Update the informed consent process. FMT recipients should be informed that healthy, asymptomatic stool donors may potentially be infected with SARS-CoV-2. Recipients should also understand the testing approach and other strategies used to mitigate the risk of SARS-CoV-2 transmission, and recognize the limitations of testing and risk mitigation strategies.

Additional Reading: More detailed information on screening donors for SARS-COV-2 and testing protocols can be found in the papers below:

Babiker, A., Ingersoll, J., Adelman, M., Webster, A., Broder, K., & Stittleburg, V. et al. (2021). [Validation of High-Sensitivity Severe Acute Respiratory Syndrome Coronavirus 2 Testing for Stool—Toward the New Normal for Fecal Microbiota Transplantation](#). *Clinical And Translational Gastroenterology*, 12(6), e00363. doi: 10.14309/ctg.0000000000000363

Ianiro, G., Mullish, B., Kelly, C., Kassam, Z., Kujper, E., & Ng, S. et al. (2020). [Reorganisation of faecal microbiota transplant services during the COVID-19 pandemic](#). *Gut*, 69(9), 1555-1563. doi: 10.1136/gutjnl-2020-321829

Ng, S., Chan, F., & Chan, P. (2020). [Screening FMT donors during the COVID-19 pandemic: a protocol for stool SARS-CoV-2 viral quantification](#). *The Lancet Gastroenterology & Hepatology*, 5(7), 642-643. doi: 10.1016/s2468-1253(20)30124-2

Key Takeaway

Donor evaluation protocols—as recommended by Medical Societies, experts, and the FDA—use questionnaires, in-person clinical evaluations, and laboratory tests to screen donors for general health markers, pathogens, and health conditions that are potentially associated with the microbiome. The methods of detection and the handling of positive results as well as incidental findings is important to consider when developing a donor program. **A full description of OpenBiome’s donor evaluation criteria is listed in [Appendix 1](#)**

Variable Selection Criteria

In addition to the core, common selection criteria above, stool banks should consider the following factors when designing their screening criteria.

Frequency of Screening: Donor health should be continuously monitored throughout their donation lifetime, although the frequency of screening may vary depending on the mechanism of testing, the incubation time of illnesses, and their windows of detection. For example, many blood and stool tests can be performed twice—once before and once after the collection window—creating a bookend pair of screens. The length of the collection window may vary but is usually around 60 days. However, some tests may need to account for extended seroconversion time where individuals exposed to HIV or other pathogens may not test positive until several days after their initial infection.

As an example, in the case of HIV to account for this possibility, FMT preparations produced from stool donated less than 21 days (or the length of the seroconversion window) remain in quarantine until the donor passes screening at the end of the following collection window. Other testing, such as that for SARS-CoV-2, may need to happen more frequently—either testing donors every 14 days via nasopharyngeal swabs or directly testing each stool donation.

More information on screening and collection windows can be found in a related paper titled “[The Logistics of Donor Screening](#)”.

Testing Modalities: Laboratory tests are complicated by the fact that there may be different test modalities for each pathogen (e.g., nucleic acid testing versus enzyme immunoassay) and that such tests are typically designed for symptomatic patients rather than asymptomatic members of the general population. Thus, different testing modalities may lead to different result and testing for pathogens in solid stool instead of watery stool may decrease sensitivity. Finally, the minimum infectious dose of a pathogen as detected in stool may not be known. Because of this, the stool bank clinical team, physicians administering FMT, and FMT recipients should recognize that a

negative test for a pathogen does not fully mitigate the risk of transmission via donated material.

Stool banks should periodically update their laboratory testing as more sensitive and/or specific tests are developed. More information on testing modalities can be found in a related paper titled “The Logistics of Donor Screening”.

Permanent and Temporary Exclusion Criteria: When donors fail a screen, stool banks must decide between permanently or temporarily excluding the donor. While some indications—such as HIV and *C. difficile*—are obvious criteria for permanent exclusion other conditions—such as allergies—are not as easily categorized. Criteria for permanent exclusion will continue to be refined as the field’s knowledge of microbiome-mediated diseases increases.

In the case of temporary exclusion, stool banks must decide the length of exclusion. Stool donors should be barred from providing stool until they have become asymptomatic, resumed normal stool patterns, and passed a partial or complete re-screening. Clinical judgement should be used to determine if the window of exclusion should be extended to account for pathogen shedding that may occur even after the donor is asymptomatic. Overall, there is limited data and guidance regarding fecal shedding periods for most enteropathogens, so the practice of temporary exclusion requires further research and development.

Endemic Indications and Indications of Specific Concern: Optimal screening batteries may be different for different patient populations or geography. In general, stool banks may choose to screen for additional pathogens that are of special concern to specific patient populations, such as immunocompromised patients or children, or, conversely, decide not to screen for pathogens that are found regularly within the general population.

For example, given the high prevalence of prior exposure to Epstein-Barr virus (EBV) and cytomegalovirus (CMV), as well as the lack of reported patient events related to transmission of viral transmission, OpenBiome does not screen for these viruses. This decision is consistent with international stool banking guidelines released in 2019.³ Instead, OpenBiome assumes that donors are positive for EBV and CMV and communicates to partner physicians that prospective FMT-recipients should be informed of this screening policy. OpenBiome also includes a disclaimer regarding the lack of EBV and CMV screening on the packaging of FMT preparations. Specific patient populations who are vulnerable to EBV or CMV infection, such as immunocompromised patients, should consider sourcing FMT material from a donor that has been screened for those viruses.

New Indications: Donor evaluation criteria should be continually updated to account for discovery of new safety risks. Such risks may be infectious agents that may be transmitted through stool, such as SARS-CoV-2, or health conditions that could potentially be linked to the microbiome.

Rational Donor Selection: OpenBiome's safety and efficacy data,⁴ demonstrate that stool from any screened donor appears to be equally efficacious at treating patients with *C. difficile*. Because of this, OpenBiome does not match FMT recipients to stool donors based on particular characteristics. This may not be the case for treating other indications where patients may benefit from rational donor selection.⁵⁻⁷ Donors and their stool may be evaluated for a variety of factors including overall microbial diversity, enrichment of specific keystone taxa missing in patients, or abundance of therapeutic metabolites.

Key Takeaway:

Because the field of FMT and the microbiome is still growing, donor evaluation criteria is constantly evolving to reflect the most up-to-date knowledge. Special attention should be paid to testing modalities, as different testing options—each with specific advantages and disadvantages—may be available for pathogens or health conditions. Additionally, when data and guidance are lacking, expert clinical judgement may be required when deciding what screening tests to include in donor evaluation and how long donors who fail tests should be excluded from donating.

Appendix 1: OpenBiome Donor Evaluation Overview

Clinical Assessment

Prior to enrollment, donors (age 18-50), provide informed consent using a Stool Donation Agreement form. Donors are assessed by a registered nurse and/or supervising clinician 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
- 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; persons who have recently been hospitalized or discharged from long term care facilities; persons who regularly attend outpatient medical or surgical clinics; persons who have recently engaged in medical tourism

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)

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.

	Pathogen/Health Marker		Method	
Serological Testing	Complete blood count with differential			
	Liver Function Panel		ALT, AST, ALP, Albumin, Bilirubin (Total, direct, indirect), CBC and differential	
	HIV-1/2		IA	
	Hepatitis A, IgM		IA	
	Hepatitis B, anti-HBc, IgM antiHBc, HBsAg		IA	
	Hepatitis C (HCV antibody)		IA	
	Hepatitis E, IgM		IA	
	<i>Treponema pallidum</i>		Antibody cascading reflex	
	<i>Strongyloides</i>		EIA	
Stool Testing	SARS-CoV-2		RT-PCR	
	<i>Clostridium difficile</i> (Toxin A/B)		PCR	
	Common enteric pathogens	<i>Campylobacter spp</i>		PCR
		<i>Salmonella spp.</i>		PCR
		<i>Shigella spp.</i>		PCR
		<i>Vibrio spp.</i>		PCR
	Diarrheagenic <i>E. coli</i>	STEC		PCR
		EPEC		PCR
		EAEC		PCR
		ETEC		PCR
		EIEC		PCR
	Multi-Drug Resistant Organisms	VRE		Culture
		ESBL		Culture
		CRE		Culture
	<i>Yersinia enterocolitica</i>		PCR	
	<i>Plesiomonas shigelloides</i>		PCR	
	<i>Helicobacter pylori</i>		EIA	
	Ova and parasites		Microscopic exam	
	<i>Giardia lamblia</i>		PCR	
	<i>Cryptosporidium spp.</i>		PCR	
	<i>Cyclospora</i>		PCR	
	Isospora		Microscopic exam	
Microsporidia		PCR		
Rotavirus		PCR		
Norovirus		PCR		
Adenovirus		PCR		
Sapovirus		PCR		
Astrovirus		PCR		
Bristol Stool Type assessment		Visual		
Nasal and Nasopharyngeal Swab Tests	Multi-Drug Resistant Organisms	MRSA	Culture	

IA = Immunoassay, EIA = Enzyme immunoassay; VRE = Vancomycin-resistant enterococci; CRE = carbapenem-resistant *Enterobacteriaceae*; ESBL = Extended-spectrum beta-lactamases; RT-PCR = real-time polymerase chain reaction; PCR = polymerase chain reaction; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; ALP = Alkaline Phosphatase; CBC = Complete Blood Count

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