Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Monitoring Fecal Microbiota Transplantation Practice in a Rapidly Evolving Health and Regulatory Environment

Fecal microbiota transplantation (FMT) has demonstrated high efficacy in recurrent *Clostridioides difficile* infections (CDI).[1] However, it remains an investigational therapy that may be used by practitioners without an investigational new drug (IND) application to treat CDI not responding to standard therapies under a policy of enforcement discretion by the U.S. Food and Drug Administration (FDA).[2] This regulatory policy is driven, in part, by concerns that available safety data for FMT are inadequate, although there have been few serious short-term adverse events or infection transmissions reported in the literature to date.[3] Nevertheless, whether FMT may increase risk of conditions associated with alterations in gut microbiota such as obesity,[4] cardiovascular disease,[5] autoimmunity,[6] or cancer[7] over the long term is unknown and remains a theoretical concern based on experimental laboratory models and limited clinical data.

Published guidance from consensus conferences on donor identification and screening, optimal FMT practices and the safe operation of stool banks have aimed to establish best practices in FMT.[8,9] Although adverse events related to the procedure must be reported when FMT is being performed under FDA IND applications, the vast number of FMTs being done in the United States remain outside of the control of regulatory agencies and there is concern that infections or other complications of FMT may be under-reported. Under current FDA policy, it is the responsibility of clinicians and investigators to educate patients about the potential risks related to the procedure, including infections and the theoretical long-term risks of manipulating intestinal microbiota. No formal mechanism exists to prospectively collect short- and long-term safety data, or to determine the impact of emerging pathogens and changing regulatory requirements, on FMT practice and outcomes.

The FMT National Registry was established to fill these critical gaps in knowledge.[10] This project, which is funded by the National Institutes of Health and administered by the American Gastroenterological Association, has enrolled 437 participants across 38 sites through July 1, 2020. Early results from the registry confirm a high real-world effectiveness of the procedure and a remarkably low incidence of infections possibly related to FMT. Implementation of this study has resulted in access to a national network of FMT providers (including nonregistry sites) that can provide timely feedback on the impact of real-world events on FMT practice. Herein, we provide a summary of surveys conducted by the registry investigators that have provided key insights into the impact of regulatory policies on sites providing FMT.

In June 2019, the FDA issued a safety alert[11] on extended-spectrum beta-lactamase–producing *Escherichia coli* transmission in 2 patients, one of whom died, after FMT for non-CDI indications. The donor for these FMTs was not screened for these organisms. This alert was accompanied by new requirements for IND holders, and recommendations to non-IND sites, that donors be screened for multidrug-resistant organisms and that patients be warned of these risks. During the months between this FDA safety alert and the paper describing details around the transmission events was published in the *New England Journal of Medicine*,[12] an August 2019 survey of registry sites was conducted to understand adherence to the new FDA donor screening protocols at sites not using OpenBiome as their exclusive source of stool. Although few respondents used material from sources other than OpenBiome, those using material from local stool banks or operating under IND reported that they were already in compliance with the FDA's recommendations. By contrast, those using patient-directed donors (eg, friends or family members) reported that their sites had not screened donors about risk factors for colonization with multidrug-resistant organisms and were not testing donor stool for the specific organisms identified in the FDA safety alert. These sites either indicated plans to change donor screening and testing protocols to be in compliance with the FDA's recommendations or to begin using material from OpenBiome exclusively owing to the complexity of testing for multidrug-resistant organisms. More recently, in March 2020, the FDA issued a safety alert regarding transmission of enteropathogenic *E coli* and Shiga-toxin producing *E coli*, via donor stool sourced from OpenBiome.[13] The American Gastroenterological Association was able to rapidly communicate details regarding these infections to registry sites as well as the society membership.

The emergence of the severe acute respiratory syndrome novel coronavirus-2 (SARS-CoV-2), and concern about the potential for transmission through feces prompted another FDA safety alert on FMT and donor screening, announced in March 2020.[14] This safety alert recommended that donor stool obtained after December 1, 2019, be discarded or tested for SARS-CoV-2 before being used to treat patients. Subsequently, an international expert panel proposed additional donor screening measures, including polymerase chain reaction assays of nasopharyngeal swab samples and direct testing of donor feces once a test is available given uncertainties around the risk of transmission via FMT,[15,16] although clinical outcomes in patients who received donor stool from an infected donor or who had FMT for CDI while infected with SARS-CoV-2 have not been reported. Nevertheless, an abundance of caution is needed because SARS-CoV-2 is able to infect intestinal epithelial cells in culture[17] and viral RNA can be detected in stool where, some studies

suggest infectious virions can be isolated (recently reviewed in www.cebm.net/covid-19/sars-cov-2-and-the-role-of-orofecal-transmission-evidence-brief/). The registry sites were again surveyed in April 2020 to determine the impact of the novel coronavirus disease-19 global pandemic on FMT procedures at US sites. This investigation revealed that 27 sites (73%) had stopped performing the procedure and the majority were instead treating patients with vancomycin maintenance 19 (70%), taper 15 (56%), or fidaxomicin 14 (52%). All sites which were continuing FMT procedures during the pandemic reported using OpenBiome material rather than directed donors. This survey permitted open-ended comments from registry providers, which identified areas for further research. Areas identified included the potential for transmission by asymptomatic donors, optimal frequency of testing donors during the pandemic, potential shift to INDs over FMT, and the long-term impact of prolonged vancomycin taper versus FMT.

In June 2020, Finch Therapeutics announced positive results from its placebo-controlled phase II of an investigational oral gut microbiota product for the prevention of recurrent CDI.[18] Rebiotix recently announced completion of a phase III trial of its own donor-derived microbiota product for treatment of CDI,[19] and results from and another phase III trial of an orally administered microbiome therapeutic agent developed by Seres Health for treatment of CDI[20] are due to be released later this year. It is hoped that approval of these products and other "purified" microbial preparations will reduce concerns around donor screening and infection transmission, expanding treatment options for patients, and facilitating research around FMT for other indications. Although, in time, these products may supplant donor fecal material, it is likely that conventional full-spectrum donor-derived FMT will continue to be performed in a significant number of patients, particularly those with severe or fulminant CDI or for investigational applications, such as inflammatory bowel disease, autism spectrum disorders, or the metabolic syndrome. The FMT National Registry will continue to be an important source of long-term data on the effects of dramatic manipulation of the gut microbiome and provide rapid real-time insights into the impact of FMT developments and policy changes on clinical practice.

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Conflicts of interest
The authors have made the following disclosures: Colleen R. Kelly reports research support and site investigator for Finch Therapeutics. Loren A. Laine has nothing to disclose. Gary D. Wu has received research support from Seres Therapeutics, Intercept Pharmaceuticals, and Takeda; and is a member of the scientific advisory boards for BioCodex and Danone.

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0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2020.08.039