INTRODUCTION
The Promise and Challenges of Microbiome-Based Therapies

Diane E. Hoffmann

Over the last dozen years, there has been an explosion in the quantity of research focused on the human microbiome, i.e., the community of bacteria, fungi, protists and viruses that live in and on our body, and the role these microorganisms play in our health and wellness. Much of the attention has been on the gut microbiome as new DNA "fingerprinting" technology has allowed scientists to identify our intestinal microorganisms, most of which cannot be cultured or survive outside of the human body. The ability to identify these organisms has allowed researchers to begin to determine if changes in our microorganisms or differences across individuals in their microbiota are related to health outcomes.

New understanding of the role and function of microorganisms in our body has led to a paradigm shift in the way we think about these microbes. Once considered mainly in the context of individual pathogen interactions with the host, we now also view most resident microbes as functioning as part of a community that provides many benefits for our physiology. They perform such tasks as programming our immune system, providing nutrients for our cells, and preventing colonization by harmful bacteria and viruses. Imbalances in our microbiota, termed "dysbiosis," can lead to a number of disorders. In the gut, for example, dysbiosis has been linked to obesity, liver diseases, neurodegenerative diseases,[1] inflammatory bowel disease, colorectal cancer, and diabetes.[2]

Some of this knowledge has led to the marketing of certain foods and dietary supplements, in particular, probiotics. These products, touted as containing "good bacteria," are attractive to many consumers as a more "natural" way to stay healthy and prevent illness. In fact, the market for probiotics continues to grow at a rapid pace. Although probiotics are maintaining popularity in the marketplace, researchers and clinicians question their true effectiveness, particularly as a way of treating illness. One shortcoming of probiotics in foods or dietary supplements is their inability to "engraft," i.e., remain permanently in the body, or trigger a shift in the balance of microorganisms in the gut necessary to prevent or treat disease. This is likely due to the relatively small doses of microorganisms that are delivered in food and dietary supplement products and the fact that they are not adapted to survive in the human host and compete with the resident microbes. In order to reap the benefits, if any, of food or supplement probiotics they generally must be taken daily to maintain a healthy balance of microorganisms.

As a result of the limitations of these types of food and supplement-based probiotics, researchers have been looking at ways to deliver microorganisms more effectively. There is now great hope in the development of microbiome-based therapies to treat or prevent diseases and chronic health conditions. The range and variety of these diseases and conditions is astonishingly wide. They include infections such as *Clostridioides difficile* (previously known as *Clostridium difficile*) infection (CDI); gastrointestinal disorders such as Crohn's disease, ulcerative colitis,[3] and irritable bowel syndrome; metabolic diseases such as diabetes and obesity; neurological conditions such as Multiple Sclerosis, Parkinson disease, autism, and depression;[4] and autoimmune disorders such as rheumatoid arthritis.[5]

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One treatment that has gained some success and notoriety is that of fecal microbiota transplantation (FMT). This therapy, at its most basic, involves taking stool from a healthy individual, mixing it with saline, and administering it to a sick individual via colonoscopy, enema, or nasoenteric tube, or having the sick individual ingest it in the form of capsules. FMT has been extremely effective at treating CDI in individuals who have been unresponsive to traditional antibiotic therapies. CDI recurrence after initial antibiotic treatment causes significant morbidity in patients and is a major cost to the U.S. health care system.[6] FMT has been strongly recommended as the best available treatment for recurrent CDI by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America.[7]

The relatively small number of practitioners performing FMT 6-7 years ago was, no doubt, increased by the establishment in 2012 of a non-profit stool bank, called OpenBiome, which screens donors, tests donor stool, and prepares stool product for shipment to physicians who then administer it to their patients. OpenBiome now provides approximately 10,000 units of stool per year to over 1,000 health care institutions across the country.

The success of FMT has also attracted the attention of numerous drug developers. As of yet, no microbiome-based therapies have been approved by the U.S. Food and Drug Administration (FDA) but there are a number in clinical trials. Newer start-up companies are developing several of these products, but larger pharmaceutical companies are also investing in microbiome research and collaborating with start-ups.[8]

While the microbiota of the human gut has drawn much attention to date, microbiome research is by no means limited to the study of the intestinal populations; researchers are also studying the vaginal and skin microbiomes. They are exploring, for example, whether vaginal microbiota transplants may be effective at treating bacterial vaginosis, and whether "vaginal seeding," whereby a mother's vaginal secretions are swabbed over her caesarian-section (C-section) delivered baby, may be effective at preventing conditions associated with C-sections such as obesity, allergies, and asthma. These researchers are conducting clinical trials to test these hypotheses. Researchers are also studying the skin microbiome and attempting skin microbiota transplants to treat various skin conditions including atopic dermatitis[9] and acne.[10] Beyond these areas of research, scientists are discussing and beginning to study the possibility of oral[11] and nasal microbiota transplants.[12]

These new and potential therapies have and are creating challenges for regulators. FDA announced in 2013 that it would regulate stool for FMT as a biologic drug requiring an investigational new drug application (IND) for clinical trials. Only a few months later, FDA stepped back, stating it would exercise enforcement discretion and not require an IND for the use of fecal microbiota for transplantation to treat CDI not responding to standard therapies (rCDI). As a result, since that time, most physicians and stool banks have not obtained an IND for the performance of FMT or for the sale of stool for FMT to treat rCDI.[13] In 2014, the agency seemed to shift direction again and, in draft guidance to industry, stated that it would only exercise enforcement discretion for rCDI if the treating clinician obtained informed consent from the patient; the FMT product was obtained from a donor known to either the patient or the treating clinician; and the stool donor and product were screened and tested under the direction of the treating provider.[14] Due to some confusion about the 2014 draft guidance, in March 2016, FDA issued another draft guidance, replacing the 2014 statement, making clear that it would not extend its enforcement discretion policy to free-standing stool banks, but would allow hospital-based stool banks to continue to provide stool for rCDI without an IND.[15] While these recent draft guidance documents have indicated a change in how FDA is thinking about regulating stool product for rCDI, the guidelines have not been deemed final and FDA continues to operate under the 2013 enforcement discretion policy permitting stool banks and physicians to provide and use stool product for treatment of rCDI without an IND.

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In the midst of this regulatory uncertainty, in 2014, faculty at the University of Maryland, Baltimore (UMB) obtained funding from the National Institute for Allergies and Infectious Diseases at the National Institutes of Health[16] to assess possible regulatory frameworks for microbiota transplants. The UMB investigators included faculty members from the Schools of Law, Medicine and Pharmacy.[17] They established a larger working group of microbiome scientists, clinicians performing microbiota transplants, legal academics, food and drug law attorneys, bioethicists, and patient and industry representatives. The working group met four times over the course of three years to discuss the state of the science and research on microbiota transplants (including FMT, vaginal microbiota transplants and skin, oral and nasal microbiota transplants). In addition, the group discussed the use of such transplants in patients, the operation of microbiota banks, the development of alternative therapies, the pros and cons of the drug/biologic regulatory pathway for these new and developing therapies, and the potential use of other regulatory pathways, such as those for blood, blood products, and human cells, tissues, and cellular and tissue-based products.

The articles in this special issue are an outgrowth of the working group meetings and earlier publications.[18] Since the initial working group meeting in December of 2015, the field has evolved and researchers, clinicians, patients and regulators have gained additional knowledge, experience and understanding of the promises and challenges of microbiota transplantations. The articles in this issue reflect that evolution and learning. They include four articles on fecal microbiota transplantation and two on vaginal microbiota transplants.

In "The Impact of Regulatory Policies on the Future of Fecal Microbiota Transplantation," Alexander Khoruts, Diane Hoffmann, and Francis Palumbo explore the potential paths FDA may take in regulating FMT.[19] These include maintaining its enforcement discretion for stool product for rCDI; ending its enforcement discretion now, before it approves a new stool-based drug for rCDI; or ending its enforcement discretion once it approves a new drug for the indication. In the article, they describe the range of new stool-based products under development and the "race" for new drug approval by a handful of companies now in the latter phases of clinical trials. The authors explore the factors that may influence FDA's decision on how to regulate FMT, such as market exclusivity for orphan drugs and data exclusivity for biologics. They also suggest factors that the agency should consider in making a decision including whether the approved drug is the "same" as, or as effective as, the stool product utilized by stool banks, and the fact that patients can gain access to stool themselves without going through a stool bank or physician, i.e., the "do-it-yourself" option. Ultimately, the authors explore the impact of the different regulatory paths on patients and on innovation and research for new microbiota-based therapies. They argue that the current circumstances, where a "natural" product (i.e., stool) is on the market and successfully utilized for a medical procedure, and cannot be effectively prohibited, presents a novel regulatory situation and calls for new regulatory strategies. Toward that end, they suggest that FDA consider a "permanent" or "ongoing" IND for stool banks permitting them to continue to provide stool to clinicians to treat rCDI but requiring them to collect data on safety and efficacy that is not being collected under the current enforcement discretion policy.

The second paper, by Pilar Ossorio and Yao Zhou ("FMT and Microbial Medical Products: Generating High-Quality Evidence through Good Governance") takes the position that FDA's current policy of exercising enforcement discretion for stool products used for FMT to treat rCDI is misguided and inadequate for generating evidence on which to base regulatory determinations of safety and efficacy.[20] The authors review the existing studies on the safety and effectiveness of FMT and assert that "[d]espite professional and public enthusiasm for FMT" there is not "high-quality evidence" of the procedure's efficacy for treatment of "any disease." They define "high-quality evidence" as "data generated from clinical trials *that justifies valid causal inference about the effects of a medical intervention*" and argue that because patients and physicians were able to access stool, and did not need to wait for a new drug to be developed and approved, the evidence generated for its safety and efficacy is "low quality and potentially misleading." They further take the position that stool-derived microbial products will probably be "at least as safe" as stool and possibly more effective. The authors posit that in regulating FMT and these new microbial products, FDA's primary goal should be a governance regime that will result in the production of high-quality evidence "for any indication for which they will be used." They claim that the current approval process for new drugs and biologics is most likely to generate such evidence, but propose a change in the manner in which the FDA enforces current regulations. They recommend that the agency build off of its 2016 proposed industry guidance requiring clinicians and stool banks to obtain an IND before "undertaking FMT for any reason." Key components of their proposal are that FDA grant expanded access to stool for FMT "to treat intermediate-size patient populations with rCDI" for patients who are not eli-

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gible for participation in an on-going clinical trial or live too far away from such a trial; that "smaller, non-academic, less-well-resourced" healthcare providers and institutions not be required to obtain an IND for FMT for rCDI, and that FDA work with sponsors to develop non-RCT (randominzed control trial) studies for which those not able to participate in RCTs would be eligible.

In the third paper ("Where stool is a drug: International approaches to regulating the use of fecal microbiota for transplantation"), Alexandra Scheeler reports on a 55-country survey of regulatory approaches to FMT for rCDI.[21] She catalogs the countries' policy choices into one of four options: 1) biologic drug: highly regulated and restricted use; 2) human cell and tissue-based products: process-focused regulation; 3) medicinal products: often a provisional category with highly variable requirements and variable access based on the jurisdiction; and 4) practice of medicine: devolved oversight and unpredictable access. While she finds that no "uniform perspective on FMT classification has emerged" Scheeler takes the position that stool product used for FMT to treat rCDI should be regulated as human cells and tissues or human cellular and tissue-based products (HCT/P). She argues that the HCT/P classification "right-sizes regulatory oversight of critical process elements of donor selection and stool preparation, while permitting flexibility in indication use." Opponents of this classification, she maintains, simply argue that stool does not fit the legal definition of human cells or tissues. This was the case, for example, in the U.S., where the definition of HCT/Ps is "articles containing or consisting of human cells or tissues that are intended for implementation, transplantation, infusion or transfer into a human recipient." Products that are "secreted or extracted human products" are explicitly excluded from the definition. Because stool is secreted from the body and is made up of bacteria, not primarily human cells and tissues, it was not considered to fit within the regulatory definition of HCT/Ps. Scheeler argues that such technical definitional requirements should not be an obstacle to including stool in this regulatory category and points to the example of Belgium's policy-makers, who simply amended the legal definition of "human body material" (their equivalent of HCT/P) which initially specifically excluded stool.

Thomas Murray and Jennifer Herbst ("The Ethics of Fecal Microbiota Transplant as a Tool for Antimicrobial Stewardship Programs") bring to light a wholly different potential benefit of FMT, that of a partial solution to the emergence and growth of multi-drug resistant organisms (MDROs).[22] The standard first-line treatment for CDI is antibiotics (often vancomycin). However, some patients have multiple recurrences of CDI requiring more and longer courses of antibiotics. If they are not cured, their continuing use of antibiotics may promote the growth of MDROs. The authors describe the role of "antimicrobial stewardship programs" (ASPs) in hospitals and long-term care facilities as a tool to prevent the spread of MDROs and hypothesize that FMT may be a mechanism that ASPs in these institutions can use to reduce the incidence of MDROs across their patient populations. Potentially, FMTs could assist in this effort by being used as a "first-line" treatment rather than after several rounds of antibiotics have been tried. Implementing such a change in the indications for use of FMT would require additional research into its safety and efficacy when used earlier in the rCDI treatment regimen. While such research is currently being undertaken, Murray and Herbst examine the ethical implications of ASPs adopting FMT as a strategy to achieve their goals of MDRO reduction. To this end, they examine the ethical issues arising from two case scenarios where patients could be candidates for FMT for new indications. The first involves a 14-year old female with leukemia who is undergoing "intense chemotherapy" and was recently "treated for a blood stream infection caused by a bacterium resistant to multiple classes of antibiotics and a surveillance stool culture confirms [she] is colonized with the same MDRO." The second case involves a 73-year-old male with dementia who is diagnosed with an initial case of *C. difficile* colitis. Murray and Herbst examine each case through the lens of clinical, organizational, and research ethics elucidating the many ethical issues at play and concluding that for these novel indications ASPs should restrict the use of FMT to "structured research protocols" until more data is published to support its use beyond rCDI.

The next article on this symposium topic moves us to what Kevin DeLong, Fareeha Zulfiqar, Diane Hoffmann, Anita Tarzian, and Laura Ensign refer to as "the next frontier" — vaginal microbiota transplantation (VMT).[23] The authors describe the potential effectiveness of VMT for the treatment of bacterial vaginosis, an overgrowth of normal bacteria in the vagina that plagues between 7% and 68% of women, depending on the geographic region and the race/ethnicity of the population sampled. While the condition may be treated successfully with antibiotics, in some women it frequently recurs. In addition to causing abnormal discharge and malodour, it may make a woman more susceptible to sexually transmitted infections, including Human Immunodeficiency Virus (HIV), as well as to pelvic inflammatory disease, miscarriages and premature delivery. The authors discuss a clinical trial

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that several of them are conducting as a first step in determining whether VMT might be a feasible treatment for bacterial vaginosis by observing whether the new microorganisms delivered to a recipient will engraft and lead to a change in the recipient's vaginal microbiome. By way of comparison to FMT, the authors discuss the regulatory challenges and ethical issues that researchers conducting studies on this new potential therapy may face. Most significant are the challenges to researchers of the drug/biologic regulatory pathway. The authors speculate about the various obstacles the traditional IND process poses for a product containing a large number and variety of living organisms and compares those obstacles to those for stool product for FMT. The article concludes with an examination of the ethical issues posed by research on VMT, which include issues of group stigma potentially based on race/ethnicity and individual discrimination as regards social groups and intimate relationships.

In the last article, Noel Mueller and co-authors write about vaginal seeding ("Bacterial Baptism: Scientific, Medical, Regulatory and Ethical Issues Raised by Vaginal Seeding of C-section-born Babies").[24] This procedure involves taking a mother's vaginal secretions during labor and delivery and swabbing her cesarean-delivered baby with them immediately after birth. Researchers believe that the technique will "restore the newborn's microbiota to a state that more closely resembles that of a vaginally born baby" and by doing so reduce the risk of C-section associated diseases and conditions. Numerous studies have connected C-section delivery to a higher incidence of obesity, asthma, allergies and other immune related disorders. In this article, Mueller et al. describe a clinical trial that three of them are involved with that is enrolling subjects. The authors discuss the regulatory and ethical issues related to research and the clinical practice of vaginal seeding. The first regulatory issue presented by the research is whether or not FDA has jurisdiction to regulate the procedure and the substance that is being transferred from the mother to the newborn. While this issue has been raised in the context of FMT and VMT the authors argue that a stronger case can be made that FDA may not have jurisdiction over the performance of vaginal seeding. The procedure may well fall under the "practice of medicine" or something else altogether, as it would be very easy for a woman to do the procedure herself on her baby after delivery without the assistance of hospital personnel. The researchers also discuss the possibility of vaginal seeding being regulated like other transplanted or transferred substances such as blood and human cells and tissue products rather than as a drug/biologic to "accommodate the unique features of vaginal microbiota in the vaginal seeding process." As regards the ethical issues associated with the procedure, while researchers have not yet established either its risks or benefits, there is great interest by women who want to give their C-section delivered infants every possible benefit as they begin their lives with a higher risk of a number of chronic conditions. The authors report that their clinical trial has received considerable attention from women locally as well as in other states and the media and that they have received requests from pregnant women asking how they can do the procedure at home. In addition, some physicians have received requests to do the procedure for their patients. The authors discuss the ethical challenges physicians face from such requests ultimately recommending that physicians refuse to perform the procedure until more data is available on both its risks and benefits.

A theme that echoes from this group of papers is the need for reliable data on the risks and benefits of microbiota transplants for new indications and the need for regulatory creativity and flexibility in order to protect patients, ensure continued innovation and research, and provide access to beneficial treatment to ill patients. As with many new therapies and technologies, microbiota transplants pose challenges for regulators and present new ethical issues for researchers and practitioners.

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ers and practitioners. While patient protection and encouraging research and innovation have long been goals for FDA, patients are demanding that a third goal of patient access to beneficial treatments be considered equally meritorious. Balancing these three objectives creates continuing challenges for the future of regulatory science. The collection of articles in this symposium issue highlight exciting developments in research and clinical practice involving microbiota transplants and raise important new considerations for regulators.

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References

1. P.D. Cani, "Human Gut Microbiome: Hopes, Threats and Promises," *Gut* 67, no. 9 (2018): 1716–1725.
2. B. Kim and J. Chun, "Current Status and Future Promise of the Human Microbiome," *Pediatric Gastroenterology, Hepatology and Nutrition* 16, no. 2 (2013): 71–79.
3. Y. Song, P. Wang, and A. Parian, et al., "Where Will Fecal Microbiota Transplantation Fit in the Treatment Algorithms for Crohn's Disease and Ulcerative Colitis: A Synthesis of Completed, Ongoing and Future Trials," *Gastroenterology* 154, no. 1, Supp. (2018): S90.
4. W.J. Lee, L.D.N. Lattimer, and S. Stephen, et al., "Fecal Microbiota Transplantation: A Review of Emerging Indications beyond Relapsing Clostridium difficile Toxin Colitis," *Gastroenterology and Hepatology* 11, no. 1 (2015): 24–32.
5. X. Zhang et al., "Efficacy and Safety of Fecal Microbiota Transplantation in Patients with Rheumatoid Arthritis Refractory to Methotrexate," ClinicalTrials.gov, *available at* <https://clinicaltrials.gov/ct2/show/NCT03944096> (last visited September 25, 2019).
6. S. Zhang, S. Palazuelos-Munoz, and E.M. Balsells, et al., "Cost of Hospital Management of Clostridium difficile Infection in United States — a Meta-Analysis and Modelling Study," *BMC Infectious Diseases* 16 (2016): 447. doi: 10.1186/s12879-016-1786-6.
7. L.C. McDonald, D.N. Gerding, and S. Johnson, et al., "Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)," *Clinical Infectious Diseases* 66, no.7 (2018): e1–e48.
8. J. Merrill, "Big Pharma Embraces Microbiome Research; Partnering Poised to Follow," *The Pink Sheet* (April 20, 1015).
9. I.A. Myles, K.W. Williams, and J.D. Reckhow, et al., "Transplantation of Human Skin Microbiota in Models of Atopic Dermatitis," *JCI Insight* 1, no. 10 (2016): e86955, *available at* <https://dx.doi.org/10.1172%2Fjci.insight.86955> (last visited September 25, 2019).
10. E. Sohn, "Skin Microbiota's Community Effort," *Nature* 563 (2018): S91.
11. M.M. Nascimento, "Oral Microbiota Transplant: A Potential New Therapy for Oral Diseases," *Journal of the California Dental Association* 45, no. 10 (2017): 565–568.
12. Anders Mårtensson et al., "Sinonasal Microbiome Transplant as a Therapy for Chronic Rhinosinusitis without Nasal Polyps (CRSsNP)," ClinicalTrials.gov, *available at* <https://clinicaltrials.gov/ct2/show/NCT03122795> (last visited September 25, 2019).
13. U.S. Food and Drug Administration, "Guidance for Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies," 78 *Federal Register* 42,965 (July 18, 2013).
14. U.S. Food and Drug Administration, "Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies, March 2016," *available at* <https://www.fda.gov/media/96562/download> (last visited September 25, 2019).
15. *Id.*
16 National Institutes for Allergies and Infectious Diseases, Grant No. R21AI119633.
17. The co-investigators included Diane E. Hoffmann (PI) School of Law; Francic Palumbo, School of Pharmacy; Jacques Ravel, School of Medicine; and Mary-Clair Roghman and Eric von Rosenvinge, School of Medicine and Veteran Affairs Maryland Health Care System, Baltimore.
18. D.E. Hoffmann, F.B. Palumbo, and J. Ravel, et al., "A Proposed Definition of Microbiota Transplantation for Regulatory Purposes," *Gut Microbes* 8, no. 3 (2017): 208–213; D.E. Hoffmann, F.B. Palumbo, and J. Ravel, et al., "Improving Regulation of Microbiota Transplants," *Science* 358, no. 6369 (2017): 1390–1391.
19. A. Khoruts, D.E. Hoffmann, and F.B. Palumbo, "The Impact of Regulatory Policies on the Future of Fecal Microbiota Transplantation," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): 482-504.
20. P. Ossorio and Y. Zhou, "FMT and Microbial Medical Products: Generating High-Quality Evidence through Good Governance," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): 505-523.
21. A. Scheeler, "Where Stool is a Drug: International Approaches to Regulating the use of Fecal Microbiota for Transplantation," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): 524-540.
22. T.S. Murray and J. Herbst, "The Ethics of Fecal Microbiota Transplant as a Tool for Antimicrobial Stewardship Programs," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): 541-554.
23. K. DeLong et al., "Vaginal, "Microbiota Transplantation: The Next Frontier," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): 555-567.
24. N. Mueller et al., "Bacterial Baptism: Scientific, Medical and Regulatory Issues Raised by Vaginal Seeding of C-Section-Born Babies," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): 568-578.

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