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**The Promise
and Challenges
of Microbiome-
Based Therapies**

Guest Edited by
Diane E. Hoffmann

SYMPOSIUM 2

**Regulation of
International
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Participant
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Guest Edited by
Mark A. Rothstein
and Bartha Maria
Knoppers

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the Editor*

Cover image ©Getty Images

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Introduction

Diane E. Hoffmann

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**The Impact of Regulatory Policies
on the Future of Fecal Microbiota
Transplantation**

*Alexander Khoruts, Diane E. Hoffmann,
and Francis B. Palumbo*

In this article, the authors explore the impact of a potential future regulatory decision by FDA whether or not to continue its enforcement discretion policy allowing physicians to perform, and stool banks to sell, stool product for fecal microbiota transplantation as a treatment for recurrent *Clostridium Difficile* infection without an Investigative New Drug (IND) application. The paper looks at the Agency's regulatory options in light of the current gut microbiota based products that are in the FDA pipeline for drug approval and the potential impact and repercussions of their approval on FDA action. In laying out FDA's options we consider the implications of market exclusivity and off-label use of newly approved drugs. Ultimately, we explore the potential impact of FDA's decision on patients, research, and innovation.

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**FMT and Microbial Medical Products:
Generating High-Quality Evidence
through Good Governance**

Pilar N. Ossorio and Yao Zhou

This article argues that current data for the safety and efficacy of fecal microbiota transplants as a treatment for any indication, including recurrent *Clostridioides difficile* infection, is low-quality. It develops a governance proposal that encourages production of high-quality evidence by incentivizing well-designed RCTs of stool and stool-derived microbial products. The proposal would require that FDA change its current enforcement approach, but it would not require any change in statutes or regulations.

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**Where Stool is a Drug: International
Approaches to Regulating the use of
Fecal Microbiota for Transplantation**

Alexandra Scheeler

Regulatory agencies vary widely in their classification of FMT, with significant impact on patient access. This article conducts a global survey of national regulations and collates existing FMT classification statuses, ultimately suggesting that the human cell and tissue product designation best fits FMT's characteristics and that definitional objectives to that classification may be overcome.

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**The Ethics of Fecal Microbiota
Transplant as a Tool for Antimicrobial
Stewardship Programs**

Thomas S. Murray and Jennifer Herbst

Multidrug resistant organisms (MDROs) are a public health threat that have reduced the effectiveness of many available antibiotics. Antimicrobial stewardship programs (ASPs) have been tasked with reducing antibiotic use and therefore the emergence of MDROs. While fecal microbiota transplant (FMT) has been proposed as therapy to reduce patient colonization of MDROs, this will require additional evidence to support an expansion of the current clinical indication for FMT. This article discusses the evidence and ethics of the expanded utilization of FMT by ASPs for reasons other than severe recurrent or refractory *Clostridioides* (formerly *Clostridium*) *difficile* infection.

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Vaginal Microbiota Transplantation: The Next Frontier

Kevin DeLong, Fareeha Zulfiqar, Diane E. Hoffmann, Anita J. Tarzian, and Laura M. Ensign

The success of fecal microbiota transplantation (FMT) as a treatment for *Clostridioides difficile* infection (CDI) has stirred excitement about the potential for microbiota transplantation as a therapy for a wide range of diseases and conditions. In this article, we discuss vaginal microbiota transplantation (VMT) as “the next frontier” in microbiota transplantation and identify the medical, regulatory, and ethical challenges related to this nascent field. We further discuss what we anticipate will be the first context for testing VMT in clinical trials, prevention of the recurrence of a condition referred to as bacterial vaginosis (BV). We also compare clinical aspects of VMT with FMT and comment on how VMT may be similar to or different from FMT in ways that may affect research design and regulatory decisions.

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Bacterial Baptism: Scientific, Medical, and Regulatory Issues Raised by Vaginal Seeding of C-Section-Born Babies

Noel T. Mueller, Suchitra K. Hourigan, Diane E. Hoffmann, Lauren Levy, Erik C. von Rosenvinge, Betty Chou, and Maria-Gloria Dominguez-Bello

Several lines of evidence suggest that children born via Cesarean section (C-section) are at greater risk for adverse health outcomes including allergies, asthma and obesity. Vaginal seeding is a medical procedure in which infants born by C-section are swabbed immediately after birth with vaginal secretions from the mother. This procedure has been proposed as a way to transfer the mother's vaginal microbiome to the child, thereby restoring the natural exposure that occurs during vaginal birth that is interrupted in the case of babies born via C-section. Preliminary evidence indicates partial restoration of microbes. However, there is insufficient evidence to determine the health benefits of the procedure. Several studies, including trial, are currently underway. At the same time, in the clinic setting, doctors are increasingly being asked to by expectant mothers to have their babies seeded. This article reports on the current research on this procedure and the issues it raises for regulators, researchers, physicians, and patients.

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Regulation of International Direct-to-Participant Genomic Research: Symposium Introduction

Mark A. Rothstein and Bartha Maria Knoppers

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Introduction to the Country Reports

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Country Reports

Collected and edited by Ma'n H. Zawati

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Legal and Ethical Challenges of International Direct-to-Participant Genomic Research: Conclusions and Recommendations

Mark A. Rothstein, Ma'n H. Zawati, Laura M. Beskow, Kathleen M. Brelsford, Kyle B. Brothers, Catherine M. Hammack-Aviran, James W. Hazel, Yann Joly, Michael Lang, Dimitri Patrinos, Andrea Saltzman, and Bartha Maria Knoppers

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The Quest for Compensation for Research-Related Injury in the United States: A New Proposal

*Carolyn Riley Chapman,
Sangita Sukumaran, Geremew Tarekegne
Tsegaye, Yelena Shevchenko, and
Arthur L. Caplan*

In the U.S., there is no requirement for research sponsors to compensate human research subjects who experience injuries as a result of their participation. In this article, we review the moral justifications that compel the establishment of a better research-related injury compensation system. We explore how other countries and certain institutions within the U.S. have adopted various systems of compensation. The existence of these systems demonstrates both that the U.S. lags behind other nations in its protection of human research subjects and that the establishment of a compensation system is both practical and feasible. We then examine factors which have prevented the U.S. from establishing its own compensation system. We consider possible alternatives for the U.S. by examining the advantages and disadvantages of both established and proposed systems. We offer a new proposal that addresses the justice concerns which compel the establishment of a national compensation system, distributes the burdens of such a system on multiple stakeholders that benefit from research, and has the additional advantage of minimizing the administrative and logistical challenges associated with initiating such a system.

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Mark Barnes, Jamie Flaherty, and Barbara E. Bierer

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The Paradox of Consent for Capacity Assessments

Peter Koch

The use of decision-making capacity assessments (DMCA) in clinical medicine is an underdeveloped yet quickly growing practice. Despite the ethical and clinical importance of these assessments as a means of protecting patient autonomy, clinicians, philosophers, and ethicists have identified a number of practical and theoretical hurdles which remain unresolved.² One ethically important yet largely unaddressed issue is whether, and to what extent physicians ought to inform and obtain consent from patients prior to initiating a capacity assessment. In what follows, I address the following question: Must, or should, physicians obtain consent for capacity assessments? I argue that physicians have an ethical obligation to obtain express patient consent for capacity assessments, and in doing so, I challenge the predominant view which requires physicians to merely inform patients without obtaining consent. I then identify an underlying philosophical paradox that

complicates the clinician's duty to obtain consent: in short, consent is needed for an assessment of one's ability to consent. Finally, I recommend a practical solution to this paradox of consent for capacity assessments by proposing a model of double consent from both the patient and health care representative.

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COMMENTARY

Neal W. Dickert

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Moral Limits of Brain Organoid Research

Julian J. Koplín and Julian Savulescu

Brain organoid research raises ethical challenges not seen in other forms of stem cell research. Given that brain organoids partially recapitulate the development of the human brain, it is plausible that brain organoids could one day attain consciousness and perhaps even higher cognitive abilities. Brain organoid research therefore raises difficult questions about these organoids' moral status – questions that currently fall outside the scope of existing regulations and guidelines. This paper shows how these gaps can be addressed. We outline a moral framework for brain organoid research that can address the relevant ethical concerns without unduly impeding this important area of research.

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COMMENTARY

Gidon Felsen

Symposium articles are solicited by the guest editor for the purposes of creating a comprehensive and definitive collection of articles on a topic relevant to the study of law, medicine and ethics. Each article is peer reviewed.

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