Commentary

Ethical challenges in conducting and the clinical application of human microbiome research

Hanieh Sadat Ejtahed[1], Mojtaba Parsa[2], Bagher Larijani[3*]

1. Assistant Professor, Obesity and Eating Habits Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.
2. Assistant Professor, Medical Ethics and History of Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran; Research Center for War-affected People, Tehran University of Medical Sciences, Tehran, Iran.
3. Professor, Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; Medical Ethics and History of Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran.

Keywords: *Medical ethics; Microbiota; Fecal microbiota transplantation.*

Introduction:

The human microbiome is defined as the population of microorganisms, including bacteria, viruses, fungi and protozoan, as well as their genetic material, which live on and inside the human body as a host (1). According to the historical understanding, the general public thinks of microorganisms as pathogens and ignores the majority of harmless or beneficial species. In recent decades, emerging high-throughput sequencing technologies have caused swift advances in microbiome science, leading to dramatic changes in our understanding of ourselves, health and disease (2).

This view of the human being as a superorganism and the human body as a dynamic ecosystem has led to a more comprehensive vision of health and a paradigm shift in clinical practice and public health. In the past, a distinction was drawn between the role of envi--ronmental and genetic factors in developing diseases, and the microbial communities were defined as environmental factors; but recent evidence representing the interactions between the microbiome and the host genome underscores the need to reconsider the former as a hidden organ of the human body (3, 4).

***Corresponding Author**
Bagher Larijani*

Address: *Endocrinology and Metabolism Research Institute, North Kargar Ave., Tehran University of Medical Sciences, Tehran, Iran.*
***Postal Code**: 1411713135*
Tel: *(+98) 21 88 22 00 38*
Email: *emrc@tums.ac.ir*

Received: *6 Feb 2023*
Accepted: *19 Apr 2023*
Published: *7 Jul 2023*

Citation to this article:
Ejtahed HS, Parsa M, Larijani B. Ethical challenges in conducting and the clinical application of human microbiome research. J Med Ethics Hist Med. 2023; 16: 5.

Advances in microbiome research combined with significant progress in "-omics" technologies such as genomics, transcriptomics, proteomics and metabolomics have generated valuable insights into the fundamental impact that microbiomes have on human health, including digestion, vitamin production, immunity, child growth, development and ageing. However, our knowledge about the microbiome is still preliminary compared to its complexity and we still do not know the exact role and function of many microbes living in our bodies. Seeing as microbiome studies have come to be a hot topic in the last decade, it is essential to identify the ethical challenges raised by human microbiome studies to advise both the researchers and participants.

Challenges in Defining the Healthy Microbiome

Particular cautions should be taken in determining the clinical indications and risk-benefit assessments associated with the applications of microbiome research findings at bedside. In spite of the increasing enthusiasm to modify the human microbiome, there is no exact definition for the healthy microbiome. It should be noted that specific species of bacteria might be beneficial for one person and harmful for another. The different responses of people to bacteria make reaching a unique definition for the normal microbiome more complicated. Moreover, we must keep in mind that human microbiota undergoes daily variations and is influenced by environmental factors such as food intake and medications. All these issues make it difficult to offer a single definition for the healthy microbiome. In addition, we face ethical challenges in manipulating an individual's microbiome because any alterations may affect the surrounding community (5, 6).

Microbiome Sampling and Privacy Protection

In microbiome studies sampling is mostly done through noninvasive procedures with minimal risk, including skin brushes, oral, vaginal and nasal swabs, saliva collection, and fecal self-collection. Therefore, the risks of human microbiome research are often negligible, except for invasive sampling by endoscopy to collect and analyze the gut microbiome (4).

Since human microbial profile could provide transparent information about the individual's habits and lifestyle, sufficiency of existing regulations in protecting information privacy should be examined in microbiome studies. Moreover, considering the possibility to identify individuals based on microbial samples, it is recommended to extend the current protections of

genetic information and privacy safeguards of human tissue samples to microbiome research (4). According to an online survey on the privacy risks of microbiome studies, most people believe that the risks are similar to those associated with genome studies or medical records, and they prefer to receive detailed explanations in informed consent forms (7).

Biobanking

Biobanks as key infrastructures for microbiome research comprise another ethical aspect of human microbiome studies. The human microbiota biobanks and the associated stored clinical information may have different purposes and scopes than biobanks storing human tissue samples; however, microbiota samples provide valuable health resources with considerable potential in treating various diseases and require privacy considerations similar to human tissue samples. A growing number of stool banks have been organized by research institutes and clinics worldwide, helping to advance the goals of personalized medicine and optimize the therapeutic application of stool samples such as fecal microbiota transplantation (FMT) (5, 8).

Like other biobanks, ethical issues to be considered in microbiota biobanks are mainly focused on information privacy, informed consent, ownership of samples and associated information, secondary use of biological specimens, future benefit sharing and return of results to participants. In biobanks, it is necessary to determine who can access the samples and which related information may be shared (4, 8).

The human microbial genome, which is considered the second genome, may be as personal as the human genome, and therefore ownership of samples is a valid consideration. On the other hand, the human microbiome is a dynamic ecosystem that, unlike the human genome, is not static throughout life. Considering the lack of stability of the microbiota composition and the gradual changes in each person's eating habits and use of antibiotics and other medications, the question of sample ownership may become more complex in microbiome research. In order to clarify this issue, there are questions that need to be answered, for instance: "Is there a core microbiome for a human being?" "How permanent could changes to the human microbiome be?" and "Could microbiome changes be transmitted to offspring?". Another important issue is lack of scientific consensus over the identification capacity of human microbiome data, like human genome data. However, the dynamic nature of microbiota creates an excellent opportunity for therapeutic interventions based on

modification of microbiota. This microbiome instability makes it more clinically actionable compared to the human genome (4, 8, 9).

Disclosure of the Results of Microbiome Research

Since microbiome tests are not considered routine medical examinations, translation of human microbiome research findings and returning the results to participants is another challenge in microbial studies. It is suggested that "findings that are analytically valid, reveal an established and substantial risk of a serious health condition, and are clinically actionable" be explained to participants (8).

The clinical significance and actionability of findings are the major reasons for the disclosure of medical research results; however, in microbiome studies, the validity and reliability of findings should also be confirmed. Moreover, in some cases, microbiota tests and sequencing are done long after sampling and biobanking, and considering the instability of microbiota, the benefit of returning the results is unknown. Furthermore, it should be noted that misinterpretation or inadequate interpretation of the results is a potential risk due to a lack of appropriate knowledge about the clinical significance of microbiome findings. Therefore, before deciding to disclose or not to disclose, a risk-benefit assessment should be done to avoid creating stress for the participant on account of something we may not have a correct interpretation of. As a result, ethical guidelines and practices regarding the return of human microbiome results should be developed (8, 9).

Fecal Microbiota Transplantation (FMT) and Probiotics as Novel Therapeutic Strategies

FMT has rapidly received attention worldwide in treating recurrent and refractory *C. difficile* infection (CDI) (10 - 14). After two cases of serious infections caused by multi-drug resistant organisms in immunocompromised adults who received investigational FMT and one case of death, the Food and Drug Administration (FDA) has introduced some donor screening and testing standards regulations (15). More research is required regarding the efficacy, risk assessment, long-term safety and possible consequences of FMT. Therefore, we should proceed with caution, especially in the case of non-CDI diseases that are not responding to standard therapies. These interventions should be conducted in the context of a clinical trial (15).

One prevalent method of modulating the microbiota composition is the use of probiotic products. With increased public awareness of the health benefits and nutritional effects of fermented

foods and probiotic products, the supply and demand markets for these products are anticipated to increase. It should be considered, however, that the beneficial effects of probiotics are strain-specific and there is no fit-for-all strain since different individuals have various health statuses (16). Therefore, regulations and monitoring are needed to examine the health claims of probiotic products. Moreover, genetically modified probiotics and disease-specific use of probiotics might challenge the existing regulations, and stricter regulations and ethical considerations may be needed (17).

Safety and accurate labeling are the other ethical issues relating to probiotic foods and supplements. According to the new labeling recommendations, labels on probiotic supplements should contain the organisms in a product down to the strain level, the existing quantitative amount of probiotics expressed in colony-forming units (CFUs), and the expiration date (18).

Conclusion

Microbiome studies improve our prior perceptions regarding the interactions between microorganisms and the human body. Along with the increasing awareness of the role of dysbiosis in pathogenesis of different diseases, novel approaches to modify the composition of the microbiota are becoming widespread. We highlight the urgent need to develop ethical guidelines concerning informed consent, privacy, microbiome biobanks, disclosure of the results of microbiome research, and translation of human microbiome research into practical applications such as FMT.

Acknowledgements

The study was not funded.

Conflict of Interests

There are no competing interests to declare.

References:

1. Ejtahed HS, Soroush AR, Angoorani P, Larijani B, Hasani-Ranjbar S. Gut microbiota as a target in the pathogenesis of metabolic disorders: a new approach to novel therapeutic agents. Hormone and Metabolic Research. 2016; 48(6): 349-58.
2. Shamarina D, Stoyantcheva I, Mason CE, Bibby K, Elhaik E. Communicating the promise, risks, and ethics of large-scale, open space microbiome and metagenome research. Microbiome. 2017; 5(1):1-9.
3. Ejtahed HS, Hasani-Ranjbar S, Larijani B. Human microbiome as an approach to personalized medicine. Alternative Therapies in Health and Medicine. 2017; 23(6): 8-9.
4. Ma Y, Chen H, Lan C, Ren J. Help, hope and hype: ethical considerations of human microbiome research and applications. Protein & cell. 2018; 9(5): 404-15.
5. Rhodes R. Ethical issues in microbiome research and medicine. BMC Medicine. 2016;14(1):1-4.
6. Smith HJ. An ethical investigation into the microbiome: the intersection of agriculture, genetics, and the obesity epidemic. Gut Microbes. 2020; 12(1):1760712.
7. Shin A, Xu H. Privacy risks in microbiome research: public perspectives before and during a global pandemic. Ethics & Human Research. 2022; 44(4): 2-13.
8. Chuong KH, Hwang DM, Tullis DE, Waters VJ, Yau YC, Guttman DS, et al. Navigating social and ethical challenges of biobanking for human microbiome research. BMC Medical Ethics. 2017;18(1):1-0.
9. Lange L, Berg G, Cernava T, Champomier-Vergès MC, Charles T, Cocolin L, et al. Microbiome ethics, guiding principles for microbiome research, use and knowledge management. Environmental Microbiome. 2022; 17(1): 1-8.
10. Drekonja D, Reich J, Gezahegn S, Greer N, Shaukat A, MacDonald R, et al. Fecal microbiota transplantation for Clostridium difficile infection: a systematic review. Ann Intern Med. 2015; 162: 630–8.
11. Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent Clostridium difficile infection: a randomized trial. Ann Intern Med. 2016; 165: 609–16.

12. Staley C, Hamilton MJ, Vaughn BP, Graiziger CT, Newman KM, Kabage AJ, et al. Successful resolution of recurrent Clostridium difficile infection using freeze-dried, encapsulated fecal microbiota; pragmatic cohort study. Am J Gastroenterol. 2017; 112: 940–7.
13. Goloshchapov OV, Olekhnovich El, Sidorenko SV, Moiseev IS, Kucher MA, Fedorov DE, et al. Long-term impact of fecal transplantation in healthy volunteers. BMC Microbiol. 2019; 19: 312.
14. Sachs RE, Edelstein CA. Ensuring the safe and effective FDA regulation of fecal microbiota transplantation. J Law Biosci. 2015; 2: 396–415.
15. Grigoryan Z, Shen MJ, Twardus SW, Beuttler MM, Chen LA, Bateman-House A. Fecal microbiota transplantation: uses, questions, and ethics. Medicine in Microecology. 2020; 6: 100027.
16. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014; 11: 506-14.
17. Harrison KL, Farrell RM, Brinich MA, Highland J, Mercer M, McCormick JB, et al. 'Someone should oversee it': patient perspectives on the ethical issues arising with the regulation of probiotics. Health Expectations. 2015;18(2): 250-61.
18. Mazzantini D, Calvigioni M, Celandroni F, Lupetti A, Ghelardi E. Spotlight on the compositional quality of probiotic formulations marketed worldwide. Frontiers in microbiology. 2021;12: 693973.