

ETHICS AND THE MICROBIOME

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ABSTRACT

The human microbiome and research linked to it have become increasingly important in our discourse about allergy and asthma and numerous other diseases. Accompanying this research and its applications are a host of ethical, legal and social implications. In this article I draw on the work of experts in the field and attempt to address these issues.

INTRODUCTION

This issue of *Current Allergy and Clinical Immunology* is devoted to the microbiome and its influence on the immune system and the development of allergy. Microbial colonies in the nasal, oral and respiratory tracts have been linked to asthma and other allergic diseases. Changes in the microbiome during pregnancy and delivery, and the method of delivery, have also been linked to the health of newborns and older children. The advances in knowledge about the human microbiome and its role in health and disease suggest that deliberately influencing and controlling the microbiome may impact the incidence of disease and may also be therapeutic in some cases. These advances have also made us aware of the potential dangers of exposure to antibiotics in early childhood, with increased risk for allergic and autoimmune diseases.¹

There are a number of ethical issues accompanying microbiome research, as well as the implications of this research for society. Some of the ethical issues associated with microbiome research are:

- the selection of research participants;
- issues around informed consent and autonomy;
- the protection of participants' privacy;
- sampling methods and associated risks, and
- the return of research findings to participants.

The implications for society include the application of the research findings to the general public, the regulation of new products arising from the research and understanding of the research by the community.^{2,3}

The National Institutes of Health (NIH) Human Microbiome Project (HMP) was designed to record the DNA of the human microbiome, with the aim of trying to establish whether all humans have a common microbiome. It also aimed to determine whether the microbiome changes during the course of a person's life and whether this can be correlated with aspects of people's health.³

INFORMED CONSENT AND RESPECT FOR AUTONOMY

The greatest challenge in microbiome research is the uncertainty regarding what will be discovered, and therefore the

possible risks and benefits cannot be anticipated. This makes the informed consent process fraught with difficulty: How does one fully disclose the risks and benefits of the research to a potential research participant? A similar issue arises to that encountered in biobanking: If one is uncertain as to what future research may be done, is a general, broad consent acceptable, or is re-consenting necessary? An alternative solution has been proposed: 'meta-consent'. This involves asking the research participants to decide how they would like to provide consent for future, as yet undetermined, research.⁴ As part of the informed consent process, the participants indicate whether they would like to provide broad or specific consent if their biological material and data are to be used for another purpose in future.⁴

Ma et al propose an alternative approach to informed consent.⁵ They argue that microbiome research has the potential to promote human health while posing truly *de minimis* risk, that is 'it entails a degree of risk so low that harms are nominal and unlikely'.⁶ Therefore, they believe we should advocate for a shift from concentrating on autonomy of participants (*sic*), to the principle of "solidarity" which entails the obligation of individuals to contribute to the enterprise of biomedicine research.⁵

One of the ways in which participants' privacy and confidentiality can be protected, is the establishment of a multidisciplinary governance board comprising individuals representing medicine, science, ethics and the public, to assess proposals for future research.³

What ought researchers to do about informing study participants of individual research results? As an example, what if a participant's intestinal microbiota pattern correlates with a disease that is potentially preventable by behaviour or diet change? Or what ought researchers to do if they discover a participant is colonised with a resistant organism? What are the implications of colonisation versus infection for an individual and the community?^{3,5}

DATA-SHARING AND PROTECTION OF PRIVACY

The Human Genome Project (HGP) grappled with protection of participants' privacy in a project that was aimed at international collaboration and publicly accessible databases. Initially, this

was addressed by using de-identified data, but it soon became apparent that this was not sufficient protection, and so access to the databases had to be restricted.³ The HMP is faced with a similar dilemma: Should the data be publicly accessible so as to maximise the scientific value of the research and remove perverse incentives associated with any discoveries, or should the data-sharing policies be more restrictive? Another contentious ethical issue is the potential linking of the microbial DNA data with human DNA and clinical information.^{3,5}

Ma et al point out that human microbiome research and the clinical applications thereof are largely unregulated outside Western countries; this may increase the risk of exploitation of vulnerable research participants.⁵

SAMPLING METHODS AND RISKS

The initial HMP phase planned for sampling of five body sites from adult volunteers: mouth, skin, nose, gastrointestinal tract and vagina, together with peripheral blood samples. Because sampling of some of these areas involves invasive methods, such as endoscopy, the risks to the participants need careful assessment. The initial approach was for minimally invasive sampling only. Emanuel et al emphasise the importance of a favourable risk–benefit ratio when designing research studies.⁷ However, as Ma et al point out, many of the risks associated with human microbiome research cannot be anticipated.⁵

SOCIAL JUSTICE CONSIDERATIONS

Social justice considerations require equitable participant selection, including ethnic, geographic and socioeconomic diversity, and minimisation of risks to the participants. One of the requirements for ethically acceptable research proposed by Emanuel et al is the social value of the research.⁷ This is as important in human microbiome research as in other forms of research.

MICROBIOME AND STOOL BANKS AND OWNERSHIP ISSUES

Human microbiome biobanks have the potential to become incredibly valuable resources. Similar ethical and legal concerns apply as to biobanks storing human tissue samples. However, problems unique to microbiome biobanks include how to determine and select healthy donors, how to manage and interpret the unprecedented amount of biological data when the relevance to disease is unknown, how to externalise and collaborate with other banks and clinics nationally and internationally, and should volunteers be rewarded for giving stool samples to incentivise stool donation?⁵

The question of ownership of stools also arises, as faeces are usually considered to be waste. Hawkins and O'Doherty posed the question: 'Who owns your poop?'¹⁸ Ownership raises the issue of potential remuneration and profit-sharing in future. The problem with microbiome research is the changing nature of one's microbiota, and whether this can actually be linked to an individual over time.^{5,8}

CLINICAL APPLICATIONS OF HUMAN MICROBIOME RESEARCH

Applications of microbiome research include administration of pro- and prebiotics to preterm newborns and people with other diseases, such as irritable bowel syndrome (IBS). Most of these recommendations appear to pose relatively low risk to the recipients.

Two clinical applications of microbiome research that may carry higher risk are those of faecal microbiota transplant (FMT) and vaginal seeding.

FMT is the process whereby large quantities of intestinal microbiota are transferred from a healthy donor into the intestinal tract of a patient.⁹ One of the indications for this procedure is recurrent *Clostridium difficile* infection. The evidence for the safety of this procedure is limited and some of the concerns revolve around resultant anxiety and depression.

Vaginal seeding involves swabbing the fluid from a woman's vagina and transferring it into the mouth, eyes and skin of her newborn baby born by caesarean section. The theory is that this will decrease the risk of the infant developing asthma and allergy later in life.¹⁰ The most serious concern is that pathogenic organisms will be transferred from the woman to her infant. Infections that may be transmitted include *C trachomatis*, *N gonorrhoea*, human papilloma virus, group A streptococci and herpes simplex virus.¹⁰ The recommendation is that vaginal seeding should be carried out only as part of a research study that has been reviewed by a Research Ethics Committee, and that it is too dangerous to implement as routine practice.

PUBLIC HEALTH CONCERNS

As Ma and O'Doherty point out, our human microbiomes are inextricably linked to those of others in our family and community.^{1,5} Any manipulation of our own microbiome by taking antibiotics or changing our diet may impact others. Ma also discusses the risks of altering the microbiomes of other species, such as chickens and cattle, and the impact that this may have on human health. And finally, an intervention designed to change the microbiome in an attempt to benefit the health of the public, may predispose people to risk from other diseases. The example Ma et al use, is that trying to eradicate *Helicobacter pylori* in an attempt to reduce the incidence of peptic ulcers and gastric cancer, may in fact increase the risk of developing oesophageal diseases such as oesophageal cancer.⁵ The incidence of asthma and allergy is also increased in people without *H pylori*.¹¹

Public health policy and ethics dictate that large-scale microbiome interventions may be detrimental, and that public opinion needs to be informed regarding the potential risks, harms and benefits.

EVIDENCE-BASED MEDICINE AND THE DANGERS OF HYPE

Human microbiome research is ground-breaking and catches the public interest because it allows for 'natural' cures for disease and disease prevention. Probiotics have become big

business, both in their pure form and as additives to yoghurt and other foods. The 'hype' around the human microbiome has to be tempered with caution, as evidence for many of these interventions is still lacking.⁵ The scientific community ought to provide a balanced message that is clearly understandable to the general public. This was not evident in a 'hard-sell' lecture at one of our recent ALLSA congresses, in which a prominent scientist promoted the probiotic supplement of one of the pharmaceutical companies in a pseudo-scientific exposition. As Ma says, 'natural' and 'organic' are often interpreted to mean 'safe', 'healthier' and 'less risky', but these words are not value-free and must be interpreted with caution.¹²

Hanage warned 'microbiomics risks being drowned in a tsunami of its own hype'.¹³ He called for the following five questions to be addressed in interpreting microbiome research:¹³

1. Can experiments detect differences that matter?
2. Does the study show causation or just correlation?

3. What is the mechanism?
4. How much do experiments reflect reality?
5. Could anything else explain the results?

CONCLUSION

Human microbiome research focuses on the relationship between human beings, our microbiota and the environment. This research has the potential to explain the relationship between health and certain diseases, including the development of allergy and asthma. Technology resulting from the research offers hope for prevention strategies and interventions. However, as with any other new research, the ethical, legal and social implications (ELSI) require careful consideration and assessment. It is incumbent on us, as healthcare professionals, to interpret the research in a responsible way, and to ensure that the public is kept informed.

DECLARATIONS OF CONFLICT OF INTEREST

The author has no conflict of interest to declare.

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