



## Ethical, legal, and social considerations in conducting the Human Microbiome Project

Amy L. McGuire, James Colgrove, Simon N. Whitney, et al.

*Genome Res.* 2008 18: 1861-1864 originally published online October 29, 2008

Access the most recent version at doi:[10.1101/gr.081653.108](https://doi.org/10.1101/gr.081653.108)

---

**References** This article cites 22 articles, 6 of which can be accessed free at:  
<http://genome.cshlp.org/content/18/12/1861.full.html#ref-list-1>

### License

**Email Alerting Service** Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or [click here](#).

---

To subscribe to *Genome Research* go to:  
<https://genome.cshlp.org/subscriptions>

---

Copyright © 2008, Cold Spring Harbor Laboratory Press

# Ethical, legal, and social considerations in conducting the Human Microbiome Project

Amy L. McGuire,<sup>1,7</sup> James Colgrove,<sup>2</sup> Simon N. Whitney,<sup>3</sup> Christina M. Diaz,<sup>1</sup> Daniel Bustillos,<sup>4</sup> and James Versalovic<sup>5,6</sup>

<sup>1</sup>Center for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, Texas 77030, USA; <sup>2</sup>Mailman School of Public Health, Columbia University, New York, New York 10032, USA; <sup>3</sup>Department of Family Medicine, Baylor College of Medicine Houston, Texas 77098, USA; <sup>4</sup>Center for Health Care Ethics, Saint Louis University, St. Louis, Missouri, 63103 USA;

<sup>5</sup>Departments of Pathology, Pediatrics, Molecular Virology & Microbiology, and Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas 77030, USA; <sup>6</sup>Departments of Pathology and Pediatrics, Texas Children's Hospital, Houston, Texas 77030, USA

The early days of the genomic revolution—from the Asilomar Conference on Recombinant DNA in 1975 to the founding of the Human Genome Project in 1990—were marked by awareness among researchers, government officials, and policy makers that emerging scientific knowledge raised a host of ethical, legal, and social challenges. Scientists now undertaking research on the human microbiome—including those engaged in the National Institutes of Health's (NIH) latest Roadmap initiative, the Human Microbiome Project (HMP)—confront a similarly uncharted ethical landscape. Not only does the conduct of human microbiome research raise important ethical considerations, but the long-term implications of the HMP also present the possibility of fundamental shifts in understandings of human life and health.

The HMP is one of several international efforts to use metagenomic analysis to study human health. It is estimated that there are 10 times as many microbial cells than human cells in and on our bodies (Turnbaugh et al. 2007). We already know that human microbiota (i.e., all the microorganisms that inhabit the skin and mucous membranes) in certain sites of the body play an essential role in maintaining health and normal function (e.g., synthesis of vitamin K in the intestinal tract) (Lupp and Finlay 2005). The HMP aims to create a reference catalogue of microbial DNA that can be used as a resource to explore whether or not humans have a “core” microbiome (i.e., a microbiome that is common to all humans); whether there is stability in an individual's microbiota through different periods in that individual's life; whether there are similarities in microbiomes within families, communities, and different environments (Palmer et al. 2007); and ultimately, whether or not changes in the human microbiome can be correlated with changes in human health.

A total of \$8.2 million was awarded in 2007 to four institutions (Baylor College of Medicine, The Broad Institute, The J. Craig Venter Institute, and Washington University) to conduct the first phase of human sampling in the HMP. Samples are being collected from ~250 healthy adults from five body sites: the oral cavity, skin, nasal cavity, gastrointestinal tract, and vagina, for a total of 18 subsites for women and 15 subsites for men. Peripheral blood is also being collected for human DNA sequencing and serum banking (to evaluate possible immune responses to the microbiome). Subjects will be screened using a general health

questionnaire. Exclusion criteria for conditions that may influence the stability of the microbial environment, including taking specific medications (e.g., antibiotics, immunosuppressive agents), major dietary changes, history of cancer (exception of certain skin cancers) or chronic immune-mediated disorders (e.g., inflammatory bowel disease, psoriasis), history of chronic candidiasis (yeast infection), or active sexually transmitted diseases (e.g., gonorrhea) within the previous 2 mo for females. Children under the age of 18 and adults beyond the age of 40 will be excluded because of the need for a relatively uniform human population, especially considering the sample size and extent of potential variation within the human microbiome. Concerns about profound physiologic changes during adolescence and menopause in women also necessitate tighter boundaries to the age range. Each subject will provide at least one set of specimens within the first year, and at least 50% of these individuals are expected to participate in follow-up sampling within 12 mo of the initial sampling at all body sites. At least 10 subjects will be invited back for more extensive and invasive sampling at all body sites. All microbial DNA sequence data will be coded and released into publicly accessible databases. Clinical information that is collected will be coded and stored in a controlled-access database so that it can be correlated with analyzed data. Human DNA will be coded and stored for future analysis. Individual human DNA data will be released into controlled-access databases; aggregate data will be released into public databases.

As the first phase of the HMP gets underway, it is important that the ethical, legal, and social implications of this research are carefully studied and responsibly managed. It is also essential that the research itself is conducted according to the highest ethical standards. Drawing on the significant body of scholarship that has amassed over the past two decades, and based on the involvement of two of the authors (A.L.M. and J.V.) with the first phase of the HMP, we identify five major ethical issues associated with conducting the HMP. This list is not exhaustive, and many of these issues are implicated in other areas of genetic research, but the complexity and exploratory nature of the HMP may, in some instances, necessitate modified resolutions.

## Informed consent and respect for autonomy

Traditional legal and ethical norms for research involving human subjects require full disclosure of the nature of the research as well as the potential risks and benefits of participation (Code of Federal Regulations [CFR] Title 45, section 46 (2005), <http://www.fda.gov/oc/ohrt/>).

### <sup>7</sup>Corresponding author.

E-mail [amcguire@bcm.edu](mailto:amcguire@bcm.edu); fax (713) 798-5678.

Article published online before print. Article and publication date are at <http://www.genome.org/cgi/doi/10.1101/gr.081653.108>.

[www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm); Caulfield 2007). However, given our limited knowledge about the human microbiome, it may be challenging to identify and explain the potential risks and benefits of participating in the HMP. At first, participants in the HMP may simply be asked to accept the uncertainty inherent in conducting microbial research as a condition of participation. As human microbiome research advances, however, new risks and benefits will be discovered, necessitating changes to the consent process to protect prospective participants and development of responsible research policy to protect previously enrolled participants.

The collection of microbial DNA from multiple body sites, linked with human DNA from each individual, will also provide a tremendous resource for future research. However, our inability to predict what research may be done in the future and the potential risks associated with that research raise the important question of whether participants should be permitted to give general consent for unspecified future research and under what circumstances, if any, re-consent should be required. This issue has been much debated in other research contexts (e.g., biobanking) (Clayton 2005; Elger and Caplan 2006; Greely 2007). Some have argued that general consent for unspecified future research is acceptable as long as participants are well informed of the uncertain nature and risks of the research and strong governance structures are in place (Greely 2007; Caulfield et al. 2008).

A centralized governance body should be established for the HMP to ensure that subjects' privacy is adequately protected and that proposals for future research are consistent with the expectations and desires of participants. Membership should be multidisciplinary and should include physicians with expertise in different areas, as well as scientists, ethicists, and public representatives. This is essential in order to avoid harm, promote public trust, and respect and enhance the autonomy of research subjects.

### Informing subjects of research-related results

The question of whether and to what extent research participants ought to be informed about individual research results is currently controversial (Shalowitz and Miller 2005; Ravitsky and Wilfond 2006; Renegar et al. 2006). In the context of the HMP, researchers may, for example, discover that a research participant has an increased risk of obesity based on recent studies that have shown a correlation between intestinal microbiota and obesity (Ley et al. 2005; DiBaise et al. 2008). This particular discovery may have implications for the subject's current behavior, and returning this information to the subject would permit him or her to alter nutritional, lifestyle, and occupational factors that might eliminate or reduce the risk of obesity and associated diseases, such as type 2 diabetes. Medical interventions such as antibiotics and chemotherapy may profoundly alter the composition and spatial topography of the intestinal microbial communities, ultimately affecting health and disease outcomes with respect to metabolism and weight gain, predisposition to chronic inflammation, and lifetime risk of neoplasia at mucosal surfaces. The current state of knowledge of the human microbiome is too premature to make any conclusions at this time regarding disease risk and susceptibility or how the microbiome may be altered to restore health. As the quality of the information improves with time and further research, investigators and health-care institutions will need to confront the issue of when (or if) certain data should be shared with participants or their physicians. Concerns

about the validity of the research findings and the integrity of data that are analyzed in research laboratories (not CLIA/[Clinical Laboratory Improvement Amendments] certified) should provide ample justification for caution until a sufficient body of knowledge has amassed.

The potential discovery of asymptomatic or subclinical infectious diseases or susceptibilities to them during the course of the HMP will likely incite further debate about whether researchers have an obligation to report such findings to participants, individuals they may infect, or public health authorities. There is also the potential that new infectious diseases may be identified during the course of the HMP (either by the HMP itself or by ordinary clinical surveillance and research), but their character, treatment, and prognosis might be poorly understood. It is important to consider that colonization may be difficult to distinguish from infection at mucosal surfaces. Nasopharyngeal colonization by potential pathogens such as *Staphylococcus aureus* is a prime example. Colonization may predispose an individual to local or systemic infections, but that predisposition may depend on the nature of the microbiome and the individual's genetic composition. Fluctuations in microbial populations may predispose to disease, but such patterns of the microbiome are currently unknown. Research and time will be needed to begin to unravel the implications of the wealth of data, including data pertinent to potential pathogens, in the microbiome. HMP researchers should establish a policy, and potential subjects should be informed of that policy, as to what actions will be taken in situations where the information about an evolving infectious disease is incomplete or contradictory.

Current policy leaves it up to the primary investigator and local institutional review board (IRB) to decide whether or not to return research results to participants. According to the NIH Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (NOT-OD-07-088, November 16, 2007), downstream users of genomic data are instructed to contact the primary investigator with relevant research findings so that the primary investigator can decide whether and how to communicate that information back to participants (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-013.html>). When making the decision whether to communicate results to participants, investigators should consider the validity, reliability, and clinical significance of the data. Participants should be asked up front if they would like to receive relevant research results, and all research findings that are going to be communicated to the participant should be confirmed in an approved laboratory (National Human Genome Research Institute 2005, "Ensuring the Safety and Effectiveness of New Genetic Tests," accessibility verified February 4, 2008; <http://www.genome.gov/10002404>).

The process of sample collection for the first phase of the HMP itself poses additional risks that must be carefully explained in the informed consent process. One of these risks involves the discovery of clinically relevant information about the research participant. During screening, potential participants will be tested for HIV and other sexually transmitted infections. A positive test result will exclude the individual from participating in the HMP. Investigators will likely want to inform the potential participant of the positive test result, but there is a possibility that the individual may not want to know. In the context of HIV, if test results are associated with personal identifiers, then federal policy requires that individuals be informed of their test results and that pre- and post-test counseling be provided (Department

of Health and Human Services, Office for Protection from Research Risks [1988], Policy on Informing Those Tested About HIV Serostatus; <http://www.hhs.gov/ohrp/humansubjects/guidance/hsc88jun.htm>). Although this policy is controversial, the rationale behind its adoption is that the opportunities for early intervention outweigh the right of subjects not to know their HIV status (Institutional Review Board Guidebook, Biomedical and Behavioral Research; [http://www.hhs.gov/ohrp/irb/irb\\_chapter5.htm#h10](http://www.hhs.gov/ohrp/irb/irb_chapter5.htm#h10)). Subjects who strongly oppose this policy can choose not to participate in the research. Although the PHS policy only addresses HIV-seropositive status, under the same reasoning, it should be extended to other treatable infections. Subjects should be informed early on in the consent process that testing will occur, that they will be informed of their test results, and that counseling will be provided.

If the individual is infected with a sexually transmitted infection, investigators will then have to decide whether to inform at-risk sexual or needle-sharing partners directly or to report the test results to state health authorities, who may initiate contact tracing. Some states require partner notification while others forbid it. Most states require that positive test results be reported to state health authorities. In Texas, where half of the subjects for the first phase of the HMP will be recruited, HIV status and most other sexually transmitted infections must be reported to the Texas Department of Health, but only a legal spouse can be told about a positive test result without explicit consent from the patient/subject. All other at-risk partners must be informed either by the infected individual or through the state's Partner Notification Program (Texas Health and Safety Code, sections 81.041, 81.042, and 81.051; <http://tlo2.tlc.state.tx.us/statutes/hs.toc.htm>). Similarly, in Missouri, where the remaining subjects will be recruited, HIV status and most other sexually transmitted infections must be reported to the Missouri Department of Health and Senior Services (Mo. Rev. Stat., sections 191.653, 191.671, and 191.686; <http://www.dhss.mo.gov/>). However, Missouri has not adopted specific statutes governing disclosure to third parties. It is important that researchers are familiar with these relevant state laws and that applicable reporting requirements are discussed with potential participants during the informed consent process.

## Data sharing and protection of privacy

Privacy is a major concern for research participants, particularly in the area of genetic research. In an effort to maximize the scientific utility of genomic data and to stimulate international collaboration, broad data sharing policies were developed during the early stages of the Human Genome Project (Eisenberg 2000; Marshall 2001; Wellcome Trust 2003). Privacy was protected by "de-identifying" genomic data prior to sharing them in publicly accessible databases. However, as technology has advanced, it has become possible to uniquely identify individuals solely on the basis of their genomic information (Lin et al. 2004). This has raised concerns about individual privacy, stimulated debate (McGuire and Gibbs 2006; Lowrance and Collins 2007), and ultimately led to a shift in NIH policy and the creation of databases with restricted access (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-013.html>; Davis and Long 2001).

As the HMP is initiated, researchers are once again faced with the decision of whether to adopt data sharing policies that allow public access. The current plan is to deposit all human microbial DNA into publicly accessible databases (Office of Port-

folio Analysis and Strategic Initiatives. NIH Roadmap for Medical Research: Human Microbiome Project—Overview; <http://nihroadmap.nih.gov/hmp>). This maximizes the scientific utility of the data and limits intellectual property claims on microbial gene discoveries. It assumes, however, that individuals cannot be uniquely identified on the basis of their microbial DNA, an assumption that may prove false as we learn more about the nature and constitution of the human microbiome. The human microbiome may also reveal unexpected information beyond individual identity. For instance, a United States citizen might be found to contain microbiota that indicate that he or she had visited specific countries or geographic regions, thereby becoming a person of interest to the Department of Homeland Security. This scenario seems unlikely but may be a cause of concern for participants.

There is also much debate about whether and how to link microbial DNA sequence data with human DNA and clinical data. There is obviously a great scientific advantage to linking microbial DNA with human DNA, but there are risks to making this information publicly accessible. If access to human data is restricted as is currently planned, then questions about whether and how to maintain a link and who should be able to access the link must be considered. The challenges of answering these questions stem from our current lack of understanding about the identifiability of microbial DNA and its potential to reveal information that may be used in discriminatory ways or may prove stigmatizing for individuals and/or groups. It is therefore important that scientists are rigorously honest with potential subjects about the limits to privacy and the uncertain nature of the risks.

## Invasiveness of sampling and minimizing risk

In order to approve federally funded research in the United States, an IRB must ensure that risks to subjects are minimized and that they are "reasonable in relation to the anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" from the research (CFR Title 45, section 46 [2005]). One of the major challenges of designing the HMP has been deciding just how invasive the sampling must be (Grice et al. 2008). On the one hand, investigators need to ensure that sampling is deep enough to obtain scientifically useful specimens. However, invasive sampling—by endoscopy, for example—increases the risk to participants and may significantly impede enrollment. Initial sampling of participants for the first phase of the HMP will be minimally invasive and will include skin brushes/scrapes, oral swabs/saliva collection/oral brushes, nasal swabs, vaginal swabs/brushes, and fecal self-collection. After the initial sampling is complete, invasive sampling will be considered (including endoscopy) for a small cohort of individuals. The precise nature of future body sites to be sampled by invasive sampling remains to be determined. As we gain a better understanding of variation in the microbiota that inhabit different parts of the body and the scientific advantages of deep versus minimally invasive sampling, sampling techniques and associated risk-benefit assessments may change. Different options include more extensive sampling of mucosal surfaces and skin, evaluation of sterile body fluids, and tissue sampling. The concept of "relatively sterile" body fluids and tissues may need to be altered based on in-depth studies by DNA amplification and sequencing and approaches such as laparoscopic surgery. Mucosal and skin surfaces that are being evaluated in the

initial phase may be more extensively sampled by special methods, such as esophagogastroduodenal endoscopy, colonoscopy, fiber optic sinus evaluation, and skin punch biopsies. Some evaluations may be part of routine medical exams, such as screening colonoscopies or oral plaque removal. These options deserve additional consideration as research on the human microbiome progresses.

## Diversity of subjects and justice

Equitable selection of subjects is required to ensure that both the risks of research participation as well as the potential benefits are distributed fairly (CFR Title 45, section 46 [2005]). In assessing diversity, it is important to consider the purpose of the research and the setting in which it will be conducted (CFR Title 45, section 46 [2005]). The first phase of the HMP is being conducted on healthy adults between the ages of 18 and 40. Children and older adults are excluded from this first pilot phase because of scientific concerns about changes in the microbial environment early and later in life. This approach will necessarily bias the sample and will probably result in a non-representative population of participants. Efforts should therefore be made to broaden the sample as soon as it is feasible.

Investigators will seek to maximize the racial and ethnic diversity of participants. Broad diversity is important to achieve the goals of the HMP. However, concerns have been raised about the potential to draw inappropriate conclusions or invalid correlations between variations in the microbiome and race or ethnicity. These concerns are not unique to the HMP, but it is important that they are appropriately addressed and responsibly managed by participating researchers (Jorde and Wooding 2004; Bonham et al. 2005).

## Conclusion

The HMP has great potential to increase our understanding of how health and disease are affected by the complex relationship between human DNA, the environment, RNA viruses, and the DNA of the millions of microbes that live in and on our bodies. As with all innovative research, there are ethical, legal, and social challenges associated with conducting human microbiome research. The responsible and ethical management of these challenges is vital to the success of this initiative.

## References

- Bonham, V.L., Warshauer-Baker, E., and Collins, F.S. 2005. Race and ethnicity in the genome era: The complexity of the constructs. *Am. Psychol.* **60**: 9–15.
- Caulfield, T. 2007. Biobanks and blanket consent: The proper place of

- the public good and public perception rationale. *King's Law J.* **18**: 209–226.
- Caulfield, T., McGuire, A.L., Cho, M., Buchanan, J.A., Burgess, M.M., Danilczyk, U., Diaz, C.M., Fryer-Edwards, K., Green, S.K., Hodosh, M.A., et al. 2008. Research ethics recommendations for whole genome research: Consensus statement. *PLoS Biol.* **6**: e73. doi: 10.1371/journal.pbio.0060073.
- Clayton, E.W. 2005. Regulation of biobanks: Informed consent and biobanks. *J. Law Med. Ethics* **33**: 15–21.
- Davis, A. and Long, R. 2001. Pharmacogenetics research network and knowledge base: 1st annual scientific meeting. *Pharmacogenomics* **2**: 285–289.
- DiBaise, J.K., Zhang, H., Crowell, M.D., Krajmalnik-Brown, R., Decker, G.A., and Rittmann, B.E. 2008. Gut microbiota and its possible relationship with obesity. *Mayo Clin. Proc.* **83**: 460–469.
- Eisenberg, R.S. 2000. Genomics in the public domain: Strategy and policy. *Nat. Rev. Genet.* **1**: 70–74.
- Elger, B.S. and Caplan, A.L. 2006. Consent and anonymization in research involving biobanks: Differing terms and norms present serious barriers to an international framework. *EMBO Rep.* **7**: 661–666.
- Greely, H.T. 2007. The uneasy ethical and legal underpinnings of large-scale genomic biobanks. *Annu. Rev. Genomics Hum. Genet.* **8**: 343–364.
- Grice, E.A., Kong, H.H., Renaud, G., Young, A.C., NISC Comparative Sequencing Program, Bouffard, G.G., Blakesley, R.W., Wolfsberg, T.G., Turner, M.L., and Segre, J.A. 2008. A diversity profile of the human skin microbiota. *Genome Res.* **18**: 1043–1050.
- Jorde, L.B. and Wooding, S.P. 2004. Genetic variation, classification and 'race.' *Nat. Genet.* **36**: S28–S33.
- Ley, R.E., Backhed, F., Turnbaugh, P., Lozupone, C.A., Knight, R.D., and Gordon, J.I. 2005. Obesity alters gut microbial ecology. *Proc. Natl. Acad. Sci.* **102**: 11070–11075.
- Lin, Z., Owen, A.B., and Altman, R.B. 2004. Genomic research and human subject privacy. *Science* **305**: 183.
- Lowrance, W.W. and Collins, F.S. 2007. Identifiability in genomic research. *Science* **317**: 600–602.
- Lupp, C. and Finlay, B.B. 2005. Intestinal microbiota. *Curr. Biol.* **15**: R235–R236.
- Marshall, E. 2001. Bermuda rules: Community spirit, with teeth. *Science* **291**: 1192.
- McGuire, A.L. and Gibbs, R.A. 2006. No longer de-identified. *Science* **312**: 370–371.
- Palmer, C., Bik, E.M., DiGiulio, D.B., Relman, D.A., and Brown, P.O. 2007. Development of the human infant intestinal microbiota. *PLoS Biol.* **5**: e177. doi: 10.1371/journal.pbio.0050177.
- Ravitsky, V. and Wilfond, B.S. 2006. Disclosing individual genetic results to research participants. *Am. J. Bioeth.* **6**: 8–17.
- Renegar, G., Webster, C.J., Stuerzebecher, S., Harty, L., Ide, S.E., Balkite, B., Rogalski-Salter, T.A., Cohen, N., Spear, B.B., Barnes, D.M., et al. 2006. Returning genetic research results to individuals: Points to consider. *Bioethics* **20**: 24–36.
- Shalowitz, D.I. and Miller, F.G. 2005. Disclosing individual results of clinical research: Implications of respect for participants. *JAMA* **294**: 737–740.
- Turnbaugh, P.J., Ley, R.E., Hamady, M., Fraser-Liggett, C.M., Knight, R., and Gordon, J.I. 2007. The human microbiome project. *Nature* **449**: 804–810.
- Wellcome Trust. 2003. Report: Sharing data from large-scale biological research projects: A system of tripartite responsibility. <http://www.wellcome.ac.uk/About-us/Publications/Books/Biomedical-science/WTD003208.htm>. Wellcome Trust, London.

Received June 10, 2008; accepted in revised form August 1, 2008.