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Perspectives On Human Microbiome Research Ethics

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Abstract

Study of ethical, legal, and social implications (ELSI) of human microbiome research has been integral to the Human Microbiome Project (HMP). This study explores core ELSI issues that arose during the first phase of the HMP from the perspective of individuals involved in the research. We conducted semi-structured in-depth interviews with investigators and NIH employees ("investigators") involved in the HMP, and with individuals recruited to participate in the HMP Healthy Cohort Study at Baylor College of Medicine ("recruits"). We report findings related to three major ELSI issues: informed consent, data sharing, and return of results. Our findings demonstrate that investigators and recruits were similarly sensitive to these issues yet generally comfortable with study design in light of current knowledge about the microbiome.

Keywords

ethics; policy; research; human micro-biome; data sharing; informed consent; return of results; qualitative research

While human bacteria and viruses are still commonly understood as "germs," studies of the human microbial ecosystem—the "human microbiome"—are showing that our indigenous microbial flora are vital to our normal physiology. One major initiative in the field of human

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microbiome research is the Human Microbiome Project, an NIH initiative that seeks to better understand how the more than 20 million unique microbial genes (Proctor, 2011) that live in and on our bodies contribute to human health and disease. A key goal of the HMP has been to characterize the human microbiome in healthy adults and develop a reference set of microbial genome sequences (the "Healthy Cohort Study"). In order to accomplish this, microbe-laden bodily fluid, mucus, tissue, and fecal specimens were collected from 300 healthy individuals aged 18–40 at 15 body sites for males and 18 body sites for females, and analyzed through "meta-genomic" methods that provide DNA sequence information for all the genetic material found in the sample.

Since the beginning of the HMP it is has been recognized that human microbiome research, like other areas of genomics, raises ethical, legal, and social issues that deserve careful consideration (Hawkins & O'Doherty, 2011; Juengst & Huss, 2009; McGuire et al., 2008). Based on our early experiences participating in the development and initiation of the HMP and our familiarity with the extensive literature on ethical issues in the field of human genomics, we identified five major research ethics issues associated with conducting human microbiome research: informed consent and respect for autonomy; informing subjects of research-related results; data sharing and protection of privacy; invasiveness of sampling and minimizing risk; and diversity of subjects and justice (McGuire et al., 2008). In an effort to better understand the relevance of these issues to individuals involved in human microbiome research, we interviewed scientists and NIH employees involved in the HMP, and individuals who were recruited to participate in the Healthy Cohort Study at BCM. We report findings related to three issues these groups agreed were key ethical issues associated with human microbiome research: informed consent, data sharing, and return of results.

Method

Sampling Strategies and Sample Sizes

INVESTIGATORS—In addition to the Healthy Cohort Study, the NIH funded several demonstration projects as part of the HMP, which focused on understanding the relationship between disease and changes in the human microbiome, technology development projects, new tool development for computational analyses, building a central resource repository (responsible for storing HMP materials and reagents) and a Data Analysis Coordination Center (DACC; the key hub for access to and analysis of HMP-generated data), and studies of the ethical, legal, and social implications (ELSI) of human microbiome research (Peterson et al., 2009). Using a purposive sampling strategy (Creswell, 2007), we identified scientists and NIH project leaders involved in all aspects of the HMP from a publicly accessible list of HMP Research Network Meeting participants. Subsequent snowball sampling (Creswell, 2007) supplemented our recruitment efforts, for example to include scientists not directly involved with the HMP but deeply involved in human microbiome research.

In this article, we refer to scientists and NIH employees as one group ("investigators"); they worked closely together throughout the HMP, thus their concerns and perspectives did not substantially differ. Recruitment occurred during 2009–2010. Initially, we distributed e-mail invitation letters to 140 investigators. Investigators were informed in the invitation letter that their agreement to participate in the interviews constituted their informed consent. Eighty-

eight agreed to participate, 41 did not respond, and 11 declined. Of the 88 investigators who agreed to participate, 63 were interviewed in 60 distinct interviews. At the beginning of each interview, investigators were reminded that their participation was voluntary and verbal informed consent was obtained.

RECRUITS—Participants were recruited to participate in the HMP Healthy Cohort Study at Washington University in St. Louis, Missouri (WUSTL) and at Baylor College of Medicine in Houston, Texas (BCM). Individuals who were recruited to participate at BCM ("recruits") were asked if they could be re-contacted about opportunities to participate in future HMP-related research projects. We attempted to include individuals who participated in the HMP, those who were found to be ineligible for participation, and those who declined participation. However, because recruitment was done primarily through posting flyers throughout the medical center and by asking interested individuals to contact the study coordinator, it proved very difficult to identify individuals who were recruited but declined participation. Of the 182 recruits who agreed to contact, 12 were excluded because they did not provide contact information. We sent e-mail invitations to 170 recruits, inviting them to complete a brief self-administered online survey about their experiences with HMP (survey results not reported). Recruits were informed in the invitation e-mail that completion of the survey constituted their informed consent.

One hundred and three evaluable surveys were completed—70 by individuals who participated in the Healthy Cohort Study at BCM; 32 by individuals who were found to be ineligible to participate during initial screening; and only one by an individual who declined to participate in the Healthy Cohort Study at BCM. A primary objective of the survey was to facilitate recruitment for in-depth interviews. All recruits who completed the survey were asked at the end of the survey if they were willing to participate in a follow-up interview: 84 agreed. Two of these recruits were excluded because they did not provide contact information, 32 were lost to follow-up, and the remaining 50 recruits were contacted via e-mail and interviewed between July 2010 and February 2011. Of those, 41 were individuals who participated in the Healthy Cohort Study and 9 were individuals deemed ineligible for Healthy Cohort Study participation. We were not able to identify any individuals who declined participation in the Healthy Cohort Study at BCM for interviews. At the beginning of each interview, recruits were reminded that their participation was voluntary and verbal informed consent was obtained.

Data Collection and Analysis

We conducted in-depth, semi-structured interviews to explore ethical, legal, and social issues associated with human microbiome research. We developed two interview guides, one for use with investigators and the other for recruits. For investigators, we asked broad questions about ethical, legal, and social issues associated with the conduct of human microbiome research in general, for example, "What, if any, ethical, legal or social issues have you encountered while working on the HMP?" as well as more directed questions about the research process, for example, "Describe the ethical issues that are related to returning research results to subjects." For recruits, we focused on questions about the research process, for example, "What did you think about the consent process?" and "If

researchers discover something significant about your microbiome, would you like to be told about that finding?" The interview guides were amended as interviewing progressed to integrate unique issues that were raised by previous respondents.

The majority of investigator interviews took place during two HMP Research Network meetings. Additional interviews were conducted in or around Houston, Texas and Bethesda, Maryland. Interviews with recruits were conducted in-person at BCM or at another location within the Texas Medical Center.

Interviews were digitally recorded and transcribed verbatim by an independent transcription service. We analyzed qualitative data using thematic content analysis. Transcripts were independently coded by members of the research team and consensus in coding (Guest & MacQueen, 2008) was reached using ATLAS.ti (v 6.2), a qualitative data analysis software program.

All study instruments and methods were reviewed and approved by the Baylor College of Medicine Institutional Review Board and the University of Texas Health Science Center Committee for the Protection of Human Subjects.

Results

Demographic data are reported in Table 1. Investigators ranged in age from 25 to > 65 years, were mostly male (62%), and identified as White (82%) and not Hispanic (86%). The majority of recruits were 21–30 years of age (76%), female (66%), and identified as White (68%) and not Hispanic (84%). Recruits self-reported their occupations; occupations were coded into field-based categories. The majority of recruits reported they were students (56%), or held occupations in research-related (28%) or general medical fields (8%).

Investigators and recruits discussed many ethical, legal, and social issues related to human microbiome research, including philosophical issues related to what it means to be normal, issues related to the clinical translation of HMP research, and legal issues related to the regulation of probiotics (results reported elsewhere). Here we focus on three research ethics issues that have generated a lot of attention in other areas of genomics and that we hypothesized would be implicated in unique ways in human microbiome research: informed consent, data sharing, and return of results. Investigators and recruits recognized these as key ethical issues in human microbiome research, but the concerns they raised were largely not HMP-specific.

INFORMED CONSENT

Drawing from guidelines developed by the National Human Genome Research Institute (NHGRI), a template informed consent document (ICD) was used as a guide for all HMP studies involving human subjects, including the ICDs used for the Healthy Cohort Study (Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals) as well as those used for the demonstration projects. While the HMP ICDs varied across projects in terms of content and study specifics, all incorporated sections (such as those pertaining to confidentiality) that responded to human subject protection issues known to be

implicated in genomic research. These ICDs were particularly complex, however, because not only did they have to address consent for the storage and use of biological specimens and the attendant privacy risks that get implicated in genomic research, but they also had to address the physical risks associated with the complicated nature of sampling from 15–18 body sites.

INVESTIGATORS

Investigators performed a variety of roles within the HMP; therefore, not all had direct experience with the ICD or the informed consent process. Among those who reported familiarity with the ICD and the informed consent process, two themes emerged. The first concerned the content of the ICD and potential subjects' ability to understand the material presented. As one investigator explained, it is a challenge making sure all potential subjects, who are armed with varying baseline understandings of science when they consider research participation, ultimately understand what they would be consenting to, as "not everybody is as scientifically literate as we [scientists] are." (Investigator #120) Investigators recognized the complexity of the information provided in the ICD, and while some recommended that the ICD be simplified, others acknowledged that, regardless of what the form said, it was the research team's responsibility to ensure potential subjects were appropriately informed:

> Well, the burden is to properly explain [consent]. It takes patience and it takes the ability to try to understand how sophisticated or unsophisticated an individual participant is, and then match the explanation to the education level. (Investigator #142)

A second concern was the length of the document. Some investigators worried about the effectiveness and utility of lengthy ICDs. As one investigator explained:

> I often have concern that the longer you make these consent forms, the less effective...the form is because people just can't—they can't focus on reading through a 15-page document and taking out the important information. (Investigator #136)

Another similarly stated:

> ...when you are faced with a 10-page document, it's really not clear what are the points that are really important for the patient...I think, in that case, providing people with more information is actually less information. (Investigator #122)

Some investigators felt that the ICDs could undermine the consent process because when the documents are too long, potential subjects may not read them. Others worried that the document length could deter potential subjects from participation. One investigator raised this concern by describing the extensive verbiage used in ICDs to address potential risks associated with participation:

> It's off-putting...if a doctor explains to [subjects] that the study is relatively risk-free...that is not concordant with giving them a 12–14 page consent form to sign. So it's either risk-free or there are 12 pages worth of risks. (Investigator #127)

As this investigator suggested, there can be a fine line between wanting to inform potential subjects of as many details of the research as possible and not scaring them away from participation because of a daunting ICD.

Most investigators recognized the need to provide subjects with detailed information about the study and its potential risks and benefits, but some felt that it would have been beneficial to have shortened versions of the HMP ICDs to give subjects in addition to the full-length ICDs. They believed shorter documents might help potential subjects sift through the girth and complexity of the documents, which would in turn maximize understanding of necessary information, for example "...I sort of wish that I could provide some second bulleted point of one page that was like, 'In plain language this is what you've just agreed to.'" (Investigator #122)

RECRUITS

Recruits were asked for their general thoughts about informed consent within the Healthy Cohort Study and probed about specific features of the BCM Healthy Cohort Study ICD, such as content and length. The majority of the recruits recalled seeing the ICD (not all of the individuals who were ineligible made it far enough into the research process to see the ICD) and indicated they felt comfortable with both the consent process and ICD. Recruits repeatedly described the consent as "straightforward" and "standard," and claimed to understand all of the content, saying the material was well explained and easy to grasp. No recruits mentioned having trouble with the BCM Healthy Cohort Study ICD, though some admitted to only skimming the document.

To contextualize their comfort with the BCM Healthy Cohort Study ICD, recruits drew from their backgrounds in two distinct ways. First, recruits often referenced their occupational or educational experiences, such as working in research-related fields or pursuing degrees in medical or scientific professions, to substantiate their familiarity with ICDs. One graduate student who participated in the HMP, for example, grounded her impressions of the BCM Healthy Cohort Study ICD in her own experience writing an IRB protocol:

> Well, I'm pretty familiar with medical jargon so, and I've written an IRB—something similar for my own project—so I thought the language was easy to understand. The objectives were easy to understand. What was needed from the patient was easy to understand. (Recruit #213)

A research coordinator who also participated in the HMP said:

> I mean, I'm very familiar with the consent process. I write consent forms for my job so to me it's not a foreign concept at all. So I was fine with it and, you know, I saw that everything was very well indicated in the consent form and it seemed like they had all the information that was necessary in it. (Recruit #307)

Other recruits referenced previous experiences as research participants and compared the BCM Healthy Cohort Study ICD to those used for other studies. As one participant recruit said: "Yeah, it was pretty straightforward. Basic forms I've signed before." (Recruit #209) An ineligible recruit reaffirmed this, saying: "Yeah, I felt that it was on par, and it was as clear as other studies I've seen." (Recruit #271)

While recruits repeatedly claimed to be at ease with the BCM Healthy Cohort Study ICD because of their own background and experiences, some questioned whether it would be difficult for individuals who had no prior familiarity with research to understand. For example, one ineligible recruit said:

> It was pretty straightforward for me, [but] again it's a little bit of a different question to ask me because I, you know, work around some of these things so some of the terms aren't necessarily foreign to me. But for a person who, you know, happens to be a business person or something and they're not used to some of the scientific lingo or whatever, it might be a little weird. (Recruit #338)

Another participant recruit expressed:

> I know kind of more of what's going on before and after the patient versus a patient who had come in who doesn't study science, who doesn't maybe know as much about the human body as I do. They might have been overwhelmed by [the consent]. (Recruit #353)

When asked explicitly about the length of the ICD, many recruits acknowledged that the document was long, but most felt that the length was appropriate. “It is a little bit of a bulky document,” one participant recruit said, “but at the same time, I think it covered things that maybe they needed to cover.” (Recruit #204) “It was long,” an ineligible recruit also opined, “but stuff like this is going to be long. You can't really shorten it without, you know, truncating things that you actually need to tell the volunteer.” (Recruit #266) Only a small minority of recruits felt the document could have been condensed. One participant recruit spoke to this point while also raising concerns about other potential subjects’ ability to understand the material:

> I think someone without a medical or scientific background would struggle with the length of it and have a hard time grasping what the real purpose of the study was. I think it could have been condensed significantly. (Recruit #236)

Data Sharing

As in other areas of genomics, privacy-related risks, like those posed by an unintentional release of identifying information (i.e., the potential to associate data with persons), were central to the protection of human subjects in human microbiome research. Since the conceptualization of the HMP, project planners have sought to minimize privacy risks by developing a data sharing plan designed to both safeguard subjects’ personal information and enhance the utility of HMP data by making as much data as possible accessible to broad research communities. To achieve these dual goals, the HMP data sharing plan stipulated that all pre-published metagenomic (and associated) data were to be rapidly released to publicly accessible databases and that all potentially identifying data (human sequence, clinical data, transcription data, etc.) were to be rapidly released to controlled-access databases (NIH Common Fund).

INVESTIGATORS

Investigators described three key challenges associated with the HMP data sharing plan that presented real and potential consequences for the protection of subjects' privacy and for the usefulness of project data. At the root of these challenges were uncertainties about what constituted identifiable data in human microbiome research and how much safeguarding was needed to protect subjects while ensuring the data remained viable for analyses.

Human Contamination Problem—The biggest challenge investigators discussed related to data sharing in the HMP, was that human DNA, which is known to be uniquely identifying to individuals, could be inadvertently released to publicly accessible databases, described by many as the problem of "human contamination." Prior to public release, investigators removed human DNA from the metagenomic data through filtering processes that compared the 16S rRNA sequence data to known genomic and microbial sequences. Human components identified via filtering were removed and deposited in controlled-access scientific databases, while the (theoretically) human-free metagenomic data were made publicly available.

Early on, investigators discovered that human DNA was not being sufficiently filtered from the metagenomic data. Investigators worked together to develop more sophisticated filtering methods that reduced the risk of human contamination. These methods were developed during the course of our interviews, and investigators expressed mixed feelings about whether or not the new methods were effective. Some felt that the filtering achieved its intended goal and that subjects were protected:

> We were first very worried about privacy and human DNA contamination. What happens if human DNA sequences get out into the public databases? We have had to deal with that within the project. As we have made progress during the last several months, the filtering methods have improved...most of us are very comfortable now with the protection and the filtering methods that are being used. I can't say that we were all comfortable in the beginning, but as we saw the development of these filtering algorithms and the data were reviewed...I think we all got more comfortable with [it]. (Investigator #101)

Others were less assured by the filtering processes and raised concerns that the filtering efforts were not effective, either because of computational limitations or because portions of the human genome have yet to be mapped so investigators could not guarantee that no novel human DNA was being released publicly. As one investigator pointed out, even with the new filtering methods there still could be risks to subjects:

> ...with the current state of our knowledge about the human genome we can't filter out absolutely all of the human DNA sequences. How much of an ethical problem is this? Well, we don't know because we're not sure of the extent of the problem. (Investigator #113)

Others pointed out that the issue of human contamination would need to be revisited as technological and scientific advances continued to be made:

> And so the thing is, is that we go to great lengths to try to scrub out as much human DNA that's detected in any of the samples that we do sequencing on. And the worry that I have is that that's based on the best algorithms and the best detection systems that we have presently. But there's always that anticipation of five years from now, as algorithms get more sophisticated, as databases become more plentiful both on the bacterial and the human side, how do we go about differentiating those types of signals...? (Investigator #162)

Uniqueness of the Microbiome—A second concern investigators raised related to data sharing in the HMP had to do with a lack of scientific consensus over whether or not microbial DNA was uniquely identifying in ways similar to human DNA. Early research on the human microbiome suggested that bacterial communities could be unique to individuals, much like fingerprints (Fierer et al., 2010). Some investigators were skeptical of these findings and doubted that microbial DNA would ever prove to be uniquely identifying: "...given the enormity of the biome mass and the fluctuations that occur I have a hard time believing that you could identify an individual from the microbiome." (Investigator #128)

Others, however, found the idea more probable. For example, one investigator felt "quite convinced that the day will come when microbiome analysis will be fairly unique to an individual, just like their own DNA is." (Investigator #129) Investigators who believed that the human microbiome was or will prove to be unique to individuals expressed concern about subjects' privacy, given that metagenomic data were being released publicly in accordance with the HMP data sharing policy. While no one knew how this issue would play out, investigators speculated about implications subjects could face in the event that their microbial DNA was identifying, such as potential for discrimination by insurance companies.

Accessibility of Metadata—*A*lthough investigators recognized and were concerned about the privacy risks associated with broad data sharing, many also expressed frustration that much of the clinical metadata collected from HMP subjects were not more readily accessible. Most investigators voiced a general appreciation for the fact that sensitive and/or potentially identifying data needed more security, but some were concerned that setting limits on scientists' ability to compare publicly available microbial data to protected metadata posed risks to HMP research on the whole. For example, some worried that analyses conducted were limited because investigators needed access to the protected metadata in order to understand microbial data. As one investigator explained:

> So [what] the HMP and human metagenomics project, in general, have—that no genomics or comparative genomic projects had before—is that to make sense out of the data, you need to have a lot of what we call "metadata" associated with your sequences and your analysis...For metagenomics projects, it doesn't make sense to say "Well, we sequence[d] everything that was in the nose of healthy adults" because it doesn't give you much information....you need that [meta]data to make sense of anything that's going to come out of your analysis. (Investigator #109)

Other investigators worried that analyses conducted without metadata could lead to inaccurate conclusions:

> ...if the data goes out without a lot of associated metadata...the data would go out maybe without a lot of the context and it could be interpreted improperly—not because there's anything wrong with the data but just because it lacks a context... (Investigator #145)

A small minority of investigators also identified an imminent need to link subjects' germline and microbial DNA for the sake of analytic understanding. Blood samples were collected as part of the Healthy Cohort Study, with the long-term goal of linking germline DNA with microbial data. However, this was not a funded part of the project, and the mechanics of conducting such analyses with the necessary protections in place have yet to be worked out. Nevertheless, this illuminates some of the challenges that lie ahead in terms of balancing data utility and subject privacy.

RECRUITS

Recruits were largely comfortable with data sharing in the HMP and saw few privacy-related risks posed by having their data shared. They provided five justifications for why they felt comfortable with the protection of their privacy in light of the HMP's data sharing plan. First, recruits were at ease because they knew their data would be number coded and de-identified. "I became a number" (Recruit #410), one participant recruit joked. The data would be "just a numbered sample," said an ineligible recruit (Recruit #215). Recruits felt that by coding the samples they became anonymous, which provided them a sense of security and resulted in few privacy-related concerns.

Second, a large proportion of recruits cited feelings of trust as the reason for why they did not have to worry about their privacy in the HMP. Some recruits put their trust in the federal government (e.g., NIH) and its governing legal systems. For example, one participant recruit said:

> So I have no issue in term[s] of privacy, especially in this project, because it's regulated by federal agencies. There's law that protect[s] the information and the people involved. (Recruit #202)

Others placed their trust in the institution (BCM) and its individual researchers, "To me everything was good. I trust the coordinators and I trust the PIs to keep my personal information private." (Recruit #229)

Third, many recruits expressed comfort with data sharing because they felt that the privacy risks were minimal and that such risks were generally outweighed by the potential benefits that could be gained by HMP research. As one participant recruit explained:

> ...I'm kinda of the opinion that if [my genetic data] can be exploited, it will be. You know? At this point, the risks of exploitation are very, very low compared to the benefits of being a part of a research initiative that can actually further the body of knowledge. (Recruit #253)

It was clear that many recruits were more concerned about having their data utilized to help advance research than they were about privacy risks posed by data sharing, such as potential for insurance or employment discrimination or social stigmatization.

Fourth, some recruits acknowledged the potential for privacy-related risks to occur in the future but few considered the risks they identified to be of present-day concern. One ineligible recruit, for example, explained she was not concerned about the possibility of identifiability saying:

> Again, I know of issues...that people have brought up, “Oh this could be a problem in the future,” but I guess I'm not really concerned about it because I'm not really sure that it's real...I think maybe that's just because the dangers aren't really real today. (Recruit #201)

For recruits, like this one, privacy-related risks were only futuristic possibilities not yet warranting alarm.

Finally, a number of recruits indicated that they were not concerned about their privacy in the HMP because they had nothing to hide when it came to their personal health information. Many indicated that they would be more concerned about privacy-related risks and about having their data shared if they had a disease, like HIV, or some other condition that was sensitive in nature. Because most recruits, including those who were ineligible, saw themselves as healthy individuals, and because it was not yet clear how the human microbiome impacts health and disease, they found it difficult to imagine that there was anything researchers might discover that would cause them to be concerned about the protection of their information. One participant recruit spoke to this point, saying:

> ...in terms of the data they're going to find—I mean, you know—I don't know what I'm going to be hiding....unless you have some weird bacteria or pathogen that's really rare, I don't really know how it would affect my medical privacy. I just can't envision a scenario where my privacy would be compromised. (Recruit #262)

As long as recruits did not feel that they would be judged, singled out, or face stigmatization because of the information discovered about them, they did not feel privacy-related risks posed by data sharing were significant.

While recruits generally voiced feelings of comfort with the protection of their privacy, some did express specific reservations about data sharing in the HMP. The biggest reservation recruits described was not wanting insurance companies to have access to their data, just in case future understandings of the micro-biome could lead to a denial of health coverage. Others were explicit about only wanting their data used for research purposes as opposed to commercial endeavors, like product marketing. Importantly, some recruits indicated that if their data were to become identifying at some point in time, either because the microbiome was shown to be uniquely identifying or because of privacy breaches, then they would be less comfortable sharing their data in the public domain. As one ineligible recruit explained:

> If it's just data and it's not specifics about me and identifying about me, then I don't mind if researchers use it. But if it's information associated directly with me, I wouldn't want that shared outside of the research group. (Recruit #206)

A few recruits additionally said that in the event that human microbiome data were shown to be uniquely identifying, they would want to know more about who had access to their

information and what their data were being used for: "...if it...proved to be identifiable, then I would want to know what they are using it for before they use it for certain things." (Recruit #216)

Return of Results

Opportunities for research subjects to learn of results coming out of the HMP were limited. Individuals interested in knowing about study or aggregated findings were, for the most part, only given the option to independently seek out future HMP publications. There were additionally few options for subjects to obtain results as they related to them individually, beyond instances of learning about active infections, like HIV, during routine blood work or about conditions, like high blood pressure, during the eligibility screening.

INVESTIGATORS

When asked about issues related to returning research results to HMP subjects, the majority of investigators acknowledged that returning results was a key challenge in human subjects' research. It was also an issue, investigators felt, that needed to be worked out both within the HMP and in genomics, more generally. Investigators tended to focus on issues related to the return of results specific to individuals, not on aggregated results that could be returned to all study subjects. They repeatedly described three key barriers to returning individual-level results to subjects in the HMP.

The biggest barrier was, due to the relative infancy of human microbiome research, researchers simply did know yet what the data mean. Some spoke generally of the unknown nature of the human microbiome; for example, one investigator said: "...we don't know what it means, and we don't know what there is to return at this point." (Investigator #130) Others focused on the fact that data were not yet interpretable at the individual level so results would have no value for subjects: "...the data aren't incredibly meaningful right now to an individual. They are more meaningful in a population level...but for the individual right now, it's not incredibly clear." (Investigator #112)

Many investigators focused on the unknown meaning of microbial data as it related to broader understandings of health and disease. For example, one investigator said:

> I think we're at such an early stage of the study, and there are a lot of intricate interplays between [the] microbiome in our own body that we still don't understand. I don't think we should sort of make any hasty conclusion on how the microbiome is really contributing [to] our health or to certain disease states. (Investigator #150)

Others spoke more specifically about the difficulties posed by returning results that make statements about subjects' health, given that so much about the microbiome remained unknown:

> ...If I were to find out that my microbiome was really whacked out, I think that would be very concerning to me. [But] the fact is, we don't really know what "whacked out microbiome" really means. (Investigator #104)

Related to uncertainties about the role of the microbiome in health and disease, a subset of investigators additionally focused on the fact that research was beginning to show individuals could be colonized with various bacteria or pathogens, but that the delineation between colonization and infection remained unclear. As one investigator explained:

> ...I guess we don't know how much healthy people carry around pathogens.... I don't imagine finding a cultivar and then saying “wow, we've got to inform this person of the presence of this bacteria,” because for all I know it's not uncommon to be a carrier. (Investigator #124)

Descriptions of the unknown meaning of HMP data strongly contributed to investigators’ overarching sense that it was too soon to consider returning individual results to HMP subjects.

The second most cited barrier investigators identified when it came to returning individual results in the HMP pertained to communicating results to subjects in a way they could understand:

> ...The average person might not understand the meaning of all of [the results] so [results] would have to be returned in a format they can relate to. I think knowledge is power, so I think yes, we should. But it might be really complicated to do that. (Investigator #139)

> I guess the main thing would be making sure people understand...what the results mean... It's hard to imagine that a series of sequence reads would really be that useful to the average person. So, there's sort of the question of the level of detail... they'd probably want more than just a one sentence: “here's the result.” We'd have to give them some kind of analysis of what we looked at and what we found. So I think trying to figure out what level of detail and how to present it so that it's maximally informative without just sort of deluging people with a lot of information that may not make all that much sense or they may not have time to sift through. (Investigator #119)

Finally, the third barrier investigators identified when it came to the prospect of returning results to HMP subjects was a lack of clinical validation. Again, because research on the human microbiome was so new, most results were preliminary, not reproduced and not clinically validated. Investigators, therefore, felt that returning results would have been inappropriate. When asked if research results should be returned to subjects, one investigator replied:

> No, I think absolutely not.... And the reason is [the HMP is] a research project. It's not a clinical assay. So the data that's generated is not rigorous enough to make a clinical diagnosis or to inform a clinical decision...the data that you get doing the research at this stage is not clinically validated so it's not appropriate to report anything back to subjects. (Investigator #157)

RECRUITS

Recruits were asked if they would be interested in receiving research results from the Healthy Cohort Study, and if so, what types of results they would want to obtain. The

majority indicated they wanted access to some type of results. Many recruits were interested in learning about aggregated or published results from the project, as articulated by this participant recruit:

> ...I think I'd rather see collective results. Those are going to be more significant anyway.... The whole point of the study is to make a generalization about the population, so those are going to be the significant results, and those should be the ones that people are interested in seeing, and that's what I would be interested in seeing. (Recruit #431)

However, more were interested in knowing results pertaining to their own data. Recruits generally provided two reasons for wanting this information: general curiosity and the desire to learn more about their health and risk of disease. Importantly, recruits expressed a desire to receive results but did not seem to expect them. As one participant recruit explained:

> ...out of curiosity I would just like to know what's going on inside of me. Like, I don't need to know. Like, that's not why I signed up for the study. But I think that if I could somehow get that information, that it would be cool. (Recruit #268)

Most recruits understood the limited clinical utility of data generated during the course of the Healthy Cohort Study, but many anticipated that the project would eventually yield health-related results, which they wanted returned, such as “I would want to know if they found anything significant that could either help improve my health in the future or prevent me from getting some sort of disease” (Recruit #211) or “[I'd] like to know everything about me to find out exactly what diseases I'm gonna get...” (Recruit #391)

While some recruits wanted disease-risk results regardless of whether they could take preventive measures, many indicated they would only want results if disease predispositions were confirmed, if treatments were readily available, or if there was something tangible they could do on an individual level to thwart disease development. Recruits who only wanted disease-risk results conditionally, referenced the potential risks, like psychological distress, of having information about their health when there was nothing they could do about it. As one participant recruit said:

> I think I'd rather just know things I could actually do something about—that just by making some sort of change in your lifestyle you could decrease your chances of that specific outcome occurring. But I don't think I'd want to just know every small possibility, no matter how slim the chance. That would just be stressful. (Recruit #383)

As an example of the type of results they would not want to receive, some recruits specifically mentioned not wanting results indicative of Huntington's chorea because they felt knowing such information would be more distressing than interesting or helpful. Recruits were more open to knowing results indicative of different types of cancer, however, because treatment options existed and there was optimism tied to early detection.

The type of results recruits were least interested in obtaining were those of unknown meaning. Many recruits felt having access to results without interpretable significance

would be either pointless or would lead to burdensome worry. As one participant recruit explained:

> If there's that, “I don't know yet”—just being somewhat in the scientific field, things can change from day to day, so I don't know if I would want to worry myself over a “what if.” I think life's too short. (Recruit #269)

Some recruits desired having the option, for example on the ICD, to receive results, while others felt offering subjects the choice to receive results would put undue burden on the study's research team. Overall, while the majority of recruits wanted results of some kind, most were comfortable with the fact that they were not likely to receive results beyond the prospect of reading published data.

Discussion

We have presented investigators’ and recruits’ perspectives on three key research ethics issues associated with the conduct of human microbiome research: informed consent, data sharing, and return of results. We asked these individuals specifically about these three issues, hypothesizing that they would arise as important ethical challenges and be implicated in unique ways in human microbiome research. Those we spoke to agreed that these were critical issues that need to be addressed, but with few exceptions, the specific concerns they raised were not unique to human microbiome research. This is an important and reassuring finding. It suggests that our human subjects’ protections transcend field of study. It might also reflect the value of incorporating ELSI into the HMP from its beginning; ELSI researchers were involved in the HMP's conception and consulted on the study design, protocol development, and informed consent process. Issues remain, but these issues relate generally to all research involving human subjects.

For example, investigators worried the ICDs used for HMP research were too long and complex for the average research subject to understand. These concerns are not unique to human microbiome research. Others have argued more generally that ICDs in biomedical research have become too long and complex (Albala, Doyle, & Appelbaum, 2010; Sharp, 2004), especially those used for genetic research and biobanking, which poses minimal physical risks to participants (Department of Health and Human Services [DHHS], 2011). Moreover, studies show that research participants have difficulty recalling what they consented to and often do not understand the information conveyed in consent documents (Bergler et al.,1980; Joffe et al., 2001; Ormond et al., 2009). Perhaps this concern was exacerbated in the HMP because its ICDs not only had to address privacy risks associated with the storage and use of biological specimens, but they also had to address the physical risks associated with the complicated nature of sampling from 15–18 body sites. The general problem of lengthy and complex ICDs is not unique to human microbiome research. In fact, the problem is so pervasive that proposed changes to the federal regulations suggest the need for abbreviated consent documents (DHHS, 2011). It remains unclear, however, what minimum set of information short forms would include.

With regards to data sharing, evidence of the potential identifiability of the human microbiome and technical challenges associated with human contamination and the need to

develop more sophisticated filtering methods were identified during the course of the HMP. These problems may be unique to human microbiome research, but the privacy implications of them are not. For years, policy debates have focused on how to maximize the accessibility and utility of genomic data while protecting individual privacy (Homer et al., 2008; Lin, Owen, & Altman, 2004; McGuire & Gibbs, 2006). This tension is reflected in the HMP data sharing plan, which protects potentially identifiable human DNA and metadata through controlled access databases, while allowing for broader public release of microbial sequence data (NIH Common Fund). Whether microbial data will remain in the public domain will depend on developing evidence of its potential identifiability and the amount of risk that subjects are willing to assume. Some subjects in this study indicated they would like to be informed of new evidence of identifiability so they can re-evaluate their willingness to consent to public data release.

Finally, we hypothesized that unique issues would arise related to the return of research results. Because the HMP was interrogating infectious pathogens, we anticipated that findings related to communicable diseases would be discovered and questions about reporting to public health authorities would be raised. Some investigators pointed out the difficulty in interpreting the potential clinical significance of HMP results due to the unclear distinction between colonization of disease pathogens and infection, but only one investigator (no recruits) talked about the public health implications of this; most focused on whether findings from the HMP meet established criteria (Beskow et al., 2001; Fabsitz et al., 2010; National Bioethics Advisory Commission, 1999; Wolf et al., 2008) for return of results to subjects.

The fact that most of the issues raised by investigators and recruits were not unique to human microbiome research may reflect a lack of moral imagination on the part of our participants. Or, it could simply reflect the success of our human subjects protections. By integrating ELSI into the HMP from its inception, and based on past experience with other similar genomic studies, issues were able to be quickly identified and responsibly managed, averting any major ethical digressions.

This does not mean, however, that there are no unique ELSI issues associated with human microbiome research. On the contrary, this area of research raises many unique philosophical, clinical, and legal issues. For example, how does knowledge about our microbiome impact what we think it means to be healthy? Normal? Human? Who owns our microbiome and what legal and/or social implications does the answer to that question have? How should the products of microbiome research be regulated and what type of evidence should be required to substantiate health-related claims for probiotic foods, like yogurt? The individuals we interviewed raised many of these broader issues (results reported elsewhere). As this research moves forward, it will be essential to continue to monitor and address the research ethics issues that arise, but these more philosophical, clinical, and legal issues should also be explored in much more depth.

Best Practices

Participants in this study raised several concerns about the ethical implications of human microbiome research that can be addressed through alternative research practice. For example, concerns about the length and complexity of ICDs could be addressed by the implementation of simplified ICDs or the inclusion of a one-page summary of the most important information with accompanying educational materials. Some investigators in this study felt that abbreviated forms would facilitate understanding, but there is a dearth of empirical evidence to support this. There is also not much agreement on what information simplified materials should include. Thus, perhaps a more effective way to facilitate understanding and improve the informed consent process would be to structure projects like the HMP so that it is possible to have ongoing interaction and information exchange with research subjects. This would allow investigators to update subjects on new information about the risks and benefits of participation, as well as aggregate study findings, afford subjects an opportunity to change their consent over time, and enable the longitudinal collection of clinical data (Kaye et al., 2012).

Another concern that was raised related to risks posed to subjects' privacy by the potential identifiability of publicly accessible microbial data. Subjects in any research will vary in their risk tolerability; some will be willing to accept risks to their privacy in order to advance research; others will want more explicit promises of protection. The HMP Healthy Cohort Study was designed to create a community resource. As such, a primary aspect of the project is data sharing, and individuals who are not comfortable with the data sharing policies should not participate in the study. In order to make an informed decision, however, research subjects must be informed of the risks and benefits of participation and should be kept informed as new information about potential risks and benefits becomes available. This can be done by creating a mechanism to facilitate ongoing communication with subjects, as mentioned above, or by adopting a policy of transparency, where subjects can seek out new information through a public website and contact study staff if they are interested in learning more. Ideally, as new information becomes available, subjects should have a right to withdraw from study participation if they no longer judge the benefits of participation to outweigh the risks. Creating systems of ongoing interaction with subjects through participant-centric initiatives might better enable subjects to exercise their right to withdraw. However, it may be impossible to retrieve data that are shared, especially in the public domain. It is therefore important that subjects be informed about limitations to their right to withdraw. It would also be advisable to include subjects in any decisions about potential changes to the data sharing policy. This would demonstrate respect and cultivate subjects' trust in the study and in the research process more generally.

With regard to returning human microbiome research results, investigators who participated in this study described uncertainties related to the colonization of infectious disease pathogens and what should be done with such findings. New and unresolved issues related to return of results, such as this, are likely to be encountered as the field progresses. These issues should be monitored in future studies, and plans to address findings of potential interest to both subjects and the general public should be built into study design.

Investigators should also be clear to articulate their plan, if any, to return results to subjects so that the practices of return are in line with subjects' expectations.

The purpose of this study was to identify the range of perspectives on key ethical, legal, and social issues associated with human microbiome research. By interviewing individuals engaged in this research in a variety of capacities (i.e., investigators, NIH project leaders, HMP subjects, and those recruited to participate who were deemed ineligible), we were able to understand these issues from multiple perspectives, which can help inform future policy development and research ethics oversight. As in all qualitative research, this paper describes a range of perspectives as they exist in a specific time and context. Other individuals may emphasize different issues or express alternative perspectives.

Research Agenda

This study offers a first look at key research ethics issues in the context of human microbiome research. Future research should assess more diverse research subjects' perspectives, especially individuals from vulnerable or underrepresented groups, as well as patients, for example those participating in the HMP demonstration projects. Many of the recruits who participated in this study worked in health-related fields, which influenced their perspectives on these issues. They were also healthy individuals, which as they reported, influenced how they felt about certain issues, including concerns about privacy. Patients who are sick and less familiar with research may feel very differently about these issues.

As the rapidly expanding field of human microbiome research matures, the issues related to informed consent, data sharing, and return of results will change. Future research should focus on assessing these changes over time. New issues will also arise, which will require quick identification and management. Moving forward, human microbiome research agendas should continue to include mechanisms to address emergent issues.

As mentioned above, it will also be important to explore some of the more philosophical, clinical, and legal issues that are implicated in human microbiome research. These issues will have a direct impact on the clinical translation of HMP research. We strongly advocate adopting a preventative ethics approach by addressing these more downstream issues now.

Educational Implications

Our findings demonstrate that while there remain uncertainties in human microbiome research, such as the potential identifiability of the microbiome, investigators involved in the HMP were sensitive to the many ethical, legal, and social issues raised by this research and recruits were generally comfortable with the study design and trusted that they were protected from harm. Institutional review boards, institutions, and investigators engaged in research on the human microbiome should be made aware of the issues identified here, of the uncertainties that persist, and of new developments as they arise. There should be a way to continually educate these groups, for example through webinars and other educational forums. It is also critically important to maintain transparency and open communication with research subjects, especially as new findings could influence subjects' continued willingness to participate.

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Biography

Amy L. McGuire is Associate Professor of Medicine and Medical Ethics and Associate Director of Research for the Center for Medical Ethics and Health Policy at Baylor College of Medicine. This article reports findings from the “Ethical, Legal and Social Dimensions of Human Microbiome Research” project (R01HG004853, “HMP ELSI project”), a NIH-funded study of investigators and participants’ perspectives on human microbiome research. Dr. McGuire is the PI of that grant. She conceptualized and supervised this research project, participated in data collection and analysis, helped draft this manuscript, and approved the final version.

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Wendy A. Keitel has extensive experience in the design and implementation of clinical trials in diverse adult populations, including college students, healthy working adults, high-risk adults, and ambulatory elders. She was the PI of the protocol for sample collection for the HMP's Healthy Cohort Study at Baylor College of Medicine. She participated in protocol design; recruitment, obtaining informed consent, and screening of potential subjects; coordinating the large clinical team necessary for sample collection; and the collection of the samples. She was Co-Investigator on the HMP ELSI project, and helped to

coordinate participant recruitment and data collection. She edited this manuscript and approved the final version.

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TABLE 1

Demographics.

INVESTIGATORS (N=63)			
Characteristic	**characteristic Specifics**	**# of subjects**	**% of total***
age range (in years)	25-34	7	11%
	35-44	19	30%
	45-54	15	24%
	55-64	14	22%
	65+	2	3%
	Missing age data	6	10%
gender	Male	39	62%
	Female	24	38%
	Missing gender data	0	0%
Race	American Indian or Alaska Native	0	0%
	Asian American	3	5%
	Native Hawaiian or Pacific Islander	0	0%
	Black or African American	0	0%
	White	52	82%
	Other[a]	3	5%
	Missing race data	5	8%
Ethnicity	Identified as Hispanic	2	3%
	Does not identify as Hispanic	54	86%
	Missing ethnicity data	7	11%

Recruits (N=50)			
Characteristic	**Characteristic Specifics**	**# of subjects**	**% of total***
Age range (in years)	18-20	0	0%
	21-30	38	76%
	31-40	12	24%
	Missing age data	0	0%
Gender	Male	17	34%
	Female	33	66%
	Missing gender data	0	0%
Race	American Indian or Alaska Native	1	2%
	Asian American or Pacific Islander	4	8%
	Black or African American	4	8%
	White	34	68%
	Other[b]	7	14%
	Missing race data	0	0%
Ethnicity	Identified as Hispanic	8	16%
	Does not identify as Hispanic	42	84%

Characteristic	Characteristic Specifics	# of subjects	% of total*
Occupation	Missing ethnicity data	0	0%
	Student[c]	28	56%
	Medical, general[d]	4	8%
	Research-related fields[e]	14	28%
	Other[f]	3	6%
	Missing Occupation data	1	2%

*All percentages have been rounded.

[a]Investigators, Race, “Other”: includes self-report “other” categories as well as multiple race selections.

[b]Recruits, Race, “Other”: includes all self-report “other” categories.

[c]Recruits, Occupation, “Student”: includes medical students, graduate students, and general (type not specified) student identifications.

[d]Recruits, Occupation, “Medical, general”: includes assorted occupations within the medical field, such as nurse and physician.

[e]Recruits, Occupation, “Research-related fields”: includes assorted occupations with specific research capacities, such as research coordinator and laboratory manager.

[f]Recruits, Occupation, “Other”: includes teacher, small business owner, and information technology employee.