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Are Changes to the Common Rule Necessary to Address Evolving Areas of Research?:

A Case Study Focusing on the Human Microbiome Project

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Introduction

The proposed changes to the Common Rule, described in the recent Advanced Notice of Proposed Rulemaking (ANPRM),[1] come more than 20 years after the U.S. Department of Health and Human Services adopted the Rule in 1991. Since that time, human subjects research has changed in significant ways. Not only has the volume of clinical research grown dramatically, this research is now regularly conducted at multiple collaborative sites that are often outside of the United States. Research takes place not only in academic medical centers, but also at outpatient clinics, community hospitals, and other nontraditional venues. In addition, technological advances, such as sophisticated computer software programs, the Internet, social media, new research methods, and mobile applications have exponentially increased the volume of data available and the possibilities for accessing, analyzing, and sharing that data.[2] But there have been other changes in human subjects research that deserve consideration when thinking about potential changes to research regulation. The Common Rule was written at a time when "classic" biomedical research was conducted by a single researcher or research team studying the effect of an intervention (usually a drug) on a diseased population. Recently, however, there have been several initiatives that come under the rubric of "big science" — efforts to study the "vast complexity of biological systems."[3] Undoubtedly, the Human Genome Project (HGP) "is the biggest and best-known large-scale biomedical research project undertaken to date."[4] A more recent "big science" initiative is the Human Microbiome Project (HMP).[5]

> This article will explore ways in which research conducted under the HMP, like research conducted under the HGP, raises challenging issues for regulation of human subjects research, particularly issues related to subject selection and recruitment, group stigma, and informational risks. We discuss whether the current Common Rule and proposed changes adequately address these issues and whether the Common Rule is the most appropriate vehicle to provide regulatory oversight and guidance on these topics.

The HMP was launched in 2007 through a National Institutes of Health (NIH) funded initiative to examine the genes and genomes of the microorganisms that live in and on our body, e.g., on our skin, in our mouth and nose, in our gut, and in our urogenital tract (our "microbiome"). In early 2008, the European Union and China embarked on a similar initiative called the Metagenomics of the Human Intestinal Tract (Meta-HIT) project. The microorganisms being studied in these projects form communities that interact with our body. One way to understand these interactions is to picture our body, conceptually, as a

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"scaffold upon which microbes build elaborate ecosystems."[6] Goals of the HMP include identifying new ways to "determine health and predisposition to diseases [as well as defining] the parameters needed to design, implement and monitor strategies for intentionally manipulating the human microbiota, to optimize its performance in the context of an individual's physiology."[7] Some have described the goals and potential benefits of the project more expansively, stating that "[i]t is hoped that this research will lead to benefits such as: a better understanding of human nutritional requirements (including how individuals will respond to specific diets), resulting in innovative food production and distribution strategies and other public health benefits; increased knowledge of areas amenable to microbial transplantation and successful manipulation; forensic tools; and pharmaceutical improvements known as 'pharmacomicrobiomics.'"[8]

The HMP is in many ways similar to the HGP, leading some commentators to refer to the HMP as the second generation of the HGP. One writer called the HGP the "warm-up exercise" for the HMP.[9] While researchers found that our human genome contains only about 20,000 protein coding genes, our human microbiome is thought to be comprised of over "8 million unique protein-coding genes or 360 times more bacterial genes than human genes."[10] Some are referring to the combination of the two genomes as a "supergenome" and to human beings and their microorganisms as "superorganisms."

The HGP and the HMP have been, respectively, efforts to establish a "reference catalogue" of genes and microorganisms present in the "healthy" or "normal" person and then to determine changes in these components of the body associated with disease and illness. The HGP presented a variety of nontraditional issues that were not present in the classic model of one research scientist or team working in a single lab or clinic and attempting to determine the effectiveness of a new drug or device. Among others, these new issues included the ability to estimate future disease propensity, the possibility of individual and group stigma associated with the research findings, and the third-party impacts that could affect blood relatives of the research subjects.

This article will explore ways in which research conducted under the HMP, like research conducted under the HGP, raises challenging issues for regulation of human subjects research, particularly issues related to subject selection and recruitment, group stigma, and informational risks. We discuss whether the current Common Rule and proposed changes adequately address these issues and whether the Common Rule is the most appropriate vehicle to provide regulatory oversight and guidance on these topics. We begin by first describing the contours of the HMP, its goals, current status, and initial results. We focus specifically on the design and results of three early studies. Second, we describe some of the distinctive ethical issues raised by the HMP and compare them to the ethical issues related to human subjects research identified during the HGP. We assert that the ethical issues raised by the HMP are not dramatically different from those raised by the HGP; they differ in degree rather than in kind. Third, we discuss ways in which some of the proposed changes to the Common Rule discussed in the ANPRM might affect big science research projects such as the HMP and to what extent such changes are necessary. We conclude the following: (1) the current Common Rule is sufficiently robust to accommodate many of the ethical issues regarding human subjects research raised by the HGP and the HMP; (2) some of the

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proposed changes to the Common Rule may improve the efficiency of human subjects research in "big science" projects, in particular efforts to streamline IRB review when research is conducted at multiple sites; and (3) there are some risks to human subjects created by projects like the HGP and HMP such as group stigma that cannot adequately be dealt with through regulations but would be better addressed via guidance to Institutional Review Boards (IRBs) and education of IRB members, human subjects, and the public.

Studies Conducted under the HMP

NIH committed over $150 million to the HMP, which was initially intended to be a five-year effort. The bulk of the funding for the project went to two clinical centers and four sequencing centers, which were tasked with "creating a reference catalogue of microbial DNA, recruiting healthy adults for microbial sampling, and performing 16S rRNA gene analyses on bacteria from several anatomic sites."[11] This effort was referred to early on as the "Jumpstart" study[12] and then as the "Healthy Cohort Study." In addition to the Healthy Cohort Study, NIH funded a number of demonstration projects to look at the relationship between the microbiome and health and disease. Questions being pursued by scientists in both research projects include:

> How stable and resilient is an individual's micro-biota throughout one day and during his or her lifespan? How similar are the microbiomes between members of a family or members of a community, or across communities in different environments? Do all humans have an identifiable core microbiome, and if so, how is it acquired and transmitted? What affects the genetic diversity of the microbiome, and how does this diversity affect adaptation of the microorganisms and the host to markedly different lifestyles and to various physiological or pathophysiological states?[13]

Others are speculating about whether our human microbiome has evolved over time in response to our environment or our behaviors, e.g., diet, exercise, hygiene, sexual activity, travel, environmental or workplace exposures, tobacco, or drug use.

The Healthy Cohort Study

Researchers at Baylor College of Medicine in Houston, TX and Washington University in St. Louis, MO recruited subjects for the Healthy Cohort Study. Stringent inclusion and exclusion criteria were applied in order to recruit healthy subjects. Six hundred subjects were initially recruited, but half were rejected because they did not meet the inclusion criteria.[14] According to one of a series of articles in *Nature,* which described some of the initial findings of the project, the most common cause of exclusion of subjects was chronic gum disease.[15] Others were excluded for, among other things, untreated cavities, being either excessively overweight or underweight (i.e., having a body mass index greater than or equal to 35 or less than or equal to 18); vital signs outside of an acceptable range at screening visit; having taken any of a long list of drugs within the past 6 months, including large doses of commercial probiotics; use of drugs for chronic, clinically significant pulmonary, cardiovascular, gastrointestinal, hepatic, or renal function abnormality; a history of cancer; an unstable dietary history; recent history of chronic alcohol consumption;

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positive test for HIV, hepatitis B (HBV), or hepatitis C (HCV); major surgery of the gastrointestinal tract in the past five years; history of active uncontrolled gastrointestinal disorders; history of psoriasis or recurrent eczema; chronic dry mouth; gingivitis; oral abscesses, oral candidiasis, or halitosis; and a long list of skin conditions occurring at time of screening. For female subjects, exclusion criteria included: use of vaginal/vulvar medications within the previous seven days; use of combination hormone vaginal ring for contraception within the last six months; history of candidiasis, urinary tract infections, or active STDs; vulvar, vaginal or cervical dysplasia within the past five years; and vaginal pH greater than 4.5 at screening.[16]

Although the inclusion criteria included subjects ranging in age from 18–40 years old, the mean age of study participants was 26 years old[17] presumably because they were more likely to meet the stringent health-related criteria. An empirical study of individuals recruited for the study (some of whom were ultimately deemed ineligible) found that 76% of recruits were between the ages of 21 and 30; 56% were students; 68% were white; 8% were black; 8% were Asian or Pacific Islander; and 16% were Hispanic.[18]

Ultimately, 242 subjects participated in the Healthy Cohort Study. They included 129 males and 113 females. A template informed consent document was established as a guide for this project based on recommendations developed by the National Human Genome Research Institute (NHGRI) at NIH and then adapted for use by researchers at Baylor and Washington University. The women were sampled at 18 body sites, and the men were sampled at 15. The samples were taken from the skin, mouth, throat, nostrils, and feces (to represent the lower gastrointestinal tract), and, in females, three additional samples from the vagina. The subjects were “sampled up to three times over 22 months generating a total of 11,174 samples.”[19]

As a requirement for funding, researchers attempting to catalogue our “core” microbiome agreed to make their sequencing data and technical information freely available to the public.[20] An HMP data-sharing plan was established for this purpose with the dual goals of making data rapidly available to the public while also safeguarding subject privacy and preventing publication of information that could be used to identify a specific individual.[21]

The Demonstration Projects

The HMP demonstration projects are focusing on bacterial, fungal, and viral changes in microbiomes from individuals with gastrointestinal, skin, nasal tract, oral cavity, genital, urinary tract, and blood disorders. Eleven demonstration projects had been undertaken as of October 2011.[22] They included “projects on microbiome-associated gastrointestinal diseases (Crohn’s disease, ulcerative colitis, pediatric inflammatory bowel syndrome, neonatal necroticizing enterocolitis, and esophageal adenocarcinoma),… urogenital conditions (changes associated with bacterial vaginosis, reproductive history, sexual history, and circumcision), and…microbiome-associated skin diseases (eczema and psoriasis).”[23] The studies, some of which involve nearly 2,000 research subjects, include individuals ranging in age from 0–50 years old.[24] Inclusion and exclusion criteria vary across these diverse studies, but a number of the studies include children, and all include individuals with the condition under study. Many of the studies are being conducted at multiple research sites.

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Three Human Microbiome Studies

In addition to the "Healthy Cohort Study," this article describes three studies. The first is a pre-HMP study, and the latter two are demonstration projects funded under the HMP. These studies were selected in part because of the sensitive nature of the data they collected or are collecting. The first two studies were undertaken by researchers at the University of Maryland School of Medicine with colleagues from other universities.[25] The authors described the purpose of the first study (the "pre-HMP study") as "to develop an in-depth and accurate understanding of the composition and ecology of the vagina microbial ecosystem in asymptomatic, otherwise healthy women," which they stated was "an essential prerequisite for comprehending the role and ultimately the function of vaginal microbiota in reducing the risk of acquiring diseases and identifying factors that determine disease susceptibility."[26] In this pre-HMP study, research subjects included 396 sexually active, North American women from four ethnic groups (white, black, Hispanic and Asian). The subjects were equally divided between the four groups. Subjects were asked to provide vaginal swabs. Researchers determined the composition of the microbiota in each subject's swab and explored how the bacterial species composition of vaginal communities vary within and between these groups.[27] Initial findings were that, for the human vagina, there is no single core microbiota; rather there are "multiple core microbiota" that can be defined by communities of similar bacterial composition (community state types).[28] The researchers found five such types of microbiota. Perhaps the most interesting and sensitive findings were that the vaginal communities were significantly and statistically correlated with race and ethnicity. Asian and white women tended to have microbial communities dominated by *Lactobacillus sp.*, whereas Hispanic and black women were more likely to have microbial communities dominated by other species and to lack significant numbers of *Lactobacillus sp.* In addition, vaginal pH values differed between the groups, with the black and Hispanic women tending to have higher pH values than the Asian and white women. (See Table 1).

The authors of the pre-HMP study state that the difference in pH levels "is significant because the occurrence of high numbers of lactobacilli and pH < 4.5 have become synonymous with 'healthy.'"[29] In fact, the Healthy Cohort Study excluded women with a vaginal pH of greater than 4.5. The authors of the pre-HMP study stated that

> [i]f accepted at face value, this common wisdom suggests that although most Asian and white women are 'healthy', a significant proportion of asymptomatic Hispanic and black women are 'unhealthy' — a notion that seems implausible. It also begs the question of what kinds of bacterial communities should be considered 'normal' in Hispanic and black women.[30]

The authors hypothesize that the differences they observed may be due to differences in "innate and adaptive immune systems, the composition and quantity of vaginal secretions, and ligands on epithelial cell surfaces."[31] But, of greater concern is that such differences in microbial vaginal communities may be due to "personal hygiene, methods of birth control, and sexual behaviors."[32]

In the second study,[33] an HMP demonstration project, the same researchers collected vaginal samples twice weekly for 16 weeks from 32 women. Along with the samples, extensive

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personal information was collected at study entry and on a daily basis, including information about the subjects' sexual activities, medication intake, and hygiene practices. The study found that women could be classified into one of five groups based on the bacterial composition and stability of their vaginal microbiota over time. In some women, the vaginal microbial community composition changed markedly and rapidly over a short period of time, whereas in others it was relatively stable. In many cases, the functions of the vaginal microbiota, including the maintenance of an acidic pH driven by the bacterial production of lactic acid, is maintained despite changes in bacterial composition. Discussing their findings, the researchers postulated that intervals of increased susceptibility to disease may occur because of fluctuations in vaginal microbiota. The authors concluded that better knowledge of the changes in the vaginal microbiota and of the interaction between the human host and the bacteria may lead to the development of strategies to manage vaginal microbes in a way that promotes health and minimizes the use of antibiotics. These strategies will likely be highly personalized because of the need to take into account differences among individuals and the potential problems that might arise from diagnostic and therapeutic strategies based on results from studies across different racial and ethnic groups.

The third study, another HMP demonstration project, is somewhat similar to the second but instead looks at the urethral microbiome in adolescent males of different ethnic and racial groups. Researchers justify the study on the grounds that "microbiota of the anterior male urethra during adolescence is poorly described and that no data address the range of 'typical' urethral organisms during adolescence as functions of pubertal development or onset of various types of partnered sexual activity."[34] They also note that there is "marked ethnic group variation in adolescent sexual behaviors and disparity in conditions such as sexually transmitted infections."[35] Research subjects were Latino, African-American and Euro-American males ages 14–17 years old at the time of enrollment. Participants were recruited from an urban community with a high prevalence of sexually transmitted infections (STIs). Researchers are collecting longitudinal urine samples as a marker for urethral microorganisms. They also are collecting behavioral and symptomologic data on a daily basis by cell phone. The behavioral data include information about specific sexual acts, such as oral-genital, vaginal, and anal sexual exposures. Data collection from the study is ongoing, but initial results show interesting similarities between the male urethral microbiota and those found in the vagina, as well as evidence that specific types of sexual activity differently influence the urethral microbiota.[36]

All three of these projects used the guidelines established by NHGRI for informed consent, but each study had unique aspects that made informed consent somewhat challenging. This was especially true for the third study, which involved only minors and required consent procedures for both the minor participants and their parents. In that study, the usual process of acquiring a minors' assent before conducting research on an underage population was deemed insufficient because the study required careful and frequent specimen collection and because some of the participants would achieve the age of majority during the course of the study.

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Early Findings

In terms of answering some of the questions that researchers are asking about the microbiome, it appears that an individual's microbiome is generally not stable over time, although for some individuals in some parts of the body, it is relatively resilient. For example, researchers studying the vaginal microbiome have found that sexual activity can "aggressively change" the vaginal microbiota, but that in some women the microbiota returns relatively quickly to baseline, while in others, it takes considerably longer to return to its prior state. Researchers have also found that a woman's menstrual period temporarily changes the vaginal microbiota. These findings raise questions as to what is "normal" and at what time one can make that determination. In the study of adolescent males, researchers are finding that there is much more stability over time in the microbiota of the urethra (at least over a three-month period) than there is in the vaginal microbiota. Researchers suspect, however, that there may be long-term changes as a result of sexual activity in males.

> There is still a great deal we do not know about our microbiota — how it is acquired, how it changes over time, what influences its composition, and whether it predisposes us to disease or helps to keep us healthy and protected from certain diseases. As to what our microbiota can tell us about our disease susceptibility, early findings from several of the demonstration projects mentioned above indicate that there is a characteristic gut microbiota community associated with specific diseases, specifically neonatal necroticizing enterocolitis, gastric esophageal reflux disease (GERD), and pediatric inflammatory bowel syndrome.

Researchers are also finding, consistent with these results, that there is not a core human microbiome. In fact, there appears to be a significant amount of variability from individual to individual and within the same individual in different parts of the body. Results from the studies described above also indicate that there may be differences across racial and ethnic groups, although there are more likely to be commonalities, for example, in microbiota across individuals or communities that share a similar diet. As a result, although it has not yet been studied, first and second generation Asian Americans may have very different gut microbiota, while second generation Asian and Hispanic Americans living in the same community may have similar gut microbiota.

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Does the HMP Raise Unique Issues for Human Subjects Research?

In terms of whether there are new and different ethical, legal, and/or social issues that are raised by the HMP and whether they are adequately addressed by the Common Rule, we might ask whether there are any differences in the ethical issues raised by the HMP than by

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the HGP. Much effort was directed at determining whether the Common Rule was adequate to address the ethical, legal, and social issues raised by the HGP. Although NIH provided guidance to researchers on how to ethically conduct HGP research,[38] no changes to the Common Rule were made to accommodate issues raised by the HGP.

Many of the key ethical questions posed by the HGP seem similar to those raised by the HMP, including what the project will tell us about predisposition to disease, privacy and confidentiality, informational risks, and individual or group stigma. One difference between the two projects, however, may be how the genome and microbiome are acquired and change over time. Although acquired from one's parents, one's microbiota can change in significant ways over time. While our genes may change as well, via mutations, such changes are much less frequent and generally come about much more slowly. Below, we describe where we see similarities and differences between the HGP and HMP and the relevance of these differences for human subjects research. For the most part, we conclude that there are not significant differences between the two initiatives in terms of the ethical issues raised and that, where there are differences, they are more in degree than in type.

New Information about Health, Disease, and Predisposition to Disease

A potential benefit of both the HGP and HMP is to provide a better understanding of what it means to be healthy or normal. These projects represent forms of population-based research — i.e., looking at the characteristics of a population rather than an individual. By mapping or cataloguing a sample of the population, these initiatives seek to elucidate the range of genes or gene variants and/or microorganisms that are common to normal or healthy individuals. This is thought to be an important first step in understanding what changes in our genes or microorganisms might result in or predispose us to diseases.

While there is some suggestion that differences in one's microbiome can predispose one to certain diseases or unhealthy states, e.g., obesity, cancer, and Alzheimer's, the information gleaned from the HMP about predisposition to disease is likely similar to that amassed from the HGP in terms of what our genome can tell us about our likelihood of developing certain diseases. Like the human genome, there is much we do not know about the human microbiome and its significance for health and disease, and it may be premature to discuss risks or benefits with individual research subjects because current data cannot be interpreted or may be interpreted incorrectly.

Cecil Lewis et al., argue that similar to the HGP, the HMP may be promising more than it can deliver, at least in the short term. They state that "the HMP is providing intriguing health-related associations. But [the] HGP has taught us that the discovery of associations very rarely translates to direct interventions."[39] This may be in large part because association does not necessarily imply causation. David Relman, who summarized the initial findings of the HMP in an article in *Nature*, described studying the human microbiome, at least so far, as "a lesson in humility." He went on to write that "[a]lthough the HMP and MetaHIT project are revealing vast amounts of previously uncharacterized microbial diversity within our 'home turf ', the functions of these communities remain largely unknown."[40]

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The information gleaned from the HGP and HMP will rarely be definitive. Most of our diseases are a result of interactions between our genes and the environment, and it is difficult to predict with any certainty the chances of developing specific diseases. Also, because the microbiome appears to change over time, and because the resilience of certain types of microbiota varies between individuals, it may be even more difficult to predict whether someone will develop certain illnesses or diseases based solely on information about his or her microbiome at a specific point in time. Other factors such as diet, chemical exposures, and changes in behavior, which are thought to affect the composition of our microbiota, may be more predictive of disease than either human DNA or microbial DNA.

Stigmatizing Behavior

Another similarity between our genome and microbiome is that they both can tell us and others about some of our behaviors. Our microbiome, however, may tell us more about our behaviors, or tell us about different kinds of behaviors, than our genome does. For example, our microbiome could potentially provide others with information about where we have recently traveled, what we have eaten, recent chemical, environmental, and/or workplace exposures, sexual practices, and use of tobacco and other drugs (legal and illicit). This information can be highly personal and potentially stigmatizing. We might ask whether it will raise the same issues about insurance and employment discrimination raised by the HGP, and whether current laws such as the Genetic Information Nondiscrimination Act of 2008 (GINA), the Health Insurance Portability and Accountability Act of 1996 (HIPAA), or the Americans with Disabilities Act (ADA) will protect individuals identified with a particular type of microbiome as likely to be engaging in certain behaviors. In some cases, the information, such as where we have travelled or whether we have used certain controlled substances, may provide data of interest to law enforcement, including the U.S. Department of Homeland Security and the Drug Enforcement Agency.

In addition to our microbiome telling us something about our past or current behavior, it is possible that our microbiome may also influence or affect our behavior. For example, our microbiome, which includes aberrations due to infections and other exposures, might affect what we eat or how much we eat.[41] One of the researchers conducting research on the male urethra proposed something that may seem farfetched, but perhaps not impossible. He speculated that microorganisms, in their desire to survive, may influence our behavior in ways that we do not understand. He gave the example of chlamydia, an STI that needs a host to survive. If an individual continues to have sexual relations with the same partner, then he/she will not “spread” the microorganism. Could the organism possibly influence that individual to have sexual intercourse with a different partner in order for the chlamydia to survive? Examples of this kind of behavior, he indicated, exist in the animal world. A 2012 article in *The Atlantic*, “How Your Cat is Making you Crazy”, describes how a parasite called *Toxoplasma gondii*, which is excreted by cats in their feces and causes toxoplasmosis, may be transmitted from cats to humans and manipulate the human’s personality, causing him or her to behave in strange, often self-destructive ways.[42] The article states that the latent parasite “may be quietly tweaking the connections between our neurons, changing our response to frightening situations, our trust in others, how outgoing we are, and even our preference for certain scents.” The author goes on to say that “the organism contributes to

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car crashes, suicides and mental disorders such as schizophrenia."[43] So, just as people have been saying "my genes made me do it," they may also be able to say "my microbiome made me do it."

Identity

Law enforcement already uses DNA tests as a technique to identify individuals who may have committed criminal acts, but it may soon also be possible to use information gained from an individual's microbiome to identify that individual, although there is still some debate over the issue. According to a recently published article by Amy McGuire et al., at the start of the HMP, there was "a lack of scientific consensus over whether or not our 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."[44] For example, Alice Hawkins and Kieran O'Doherty state that the "composition of bacterial communities associated with human skin have been found to be unique to each individual, allowing for identification of individuals through analysis of residual skin bacteria recovered from an object (e.g., keyboard or mouse) touched by that person."[45] On the other hand, the authors acknowledge that the transient nature of our microbiomes may make it difficult to determine if microbial communities identified at one point in time are those of a specific individual. Based on interviews with HMP investigators, McGuire and her colleagues found that "[s]ome investigators… doubted that microbial DNA would ever prove to be uniquely identifying… Others, however, found the idea more probable" and were convinced that in the future researchers would find that "microbiome analysis" is "fairly unique to an individual, just like their own DNA is."[46]

Early on, researchers also expressed concern about the difficulty of removing human DNA from the microbial DNA samples collected from research subjects. This was referred to as the human contamination problem. This potential problem was addressed by using DNA analysis software to filter out the human DNA sequence data, which might contain identifiable information, from the entire DNA sequence data. While the human DNA could create issues with subject privacy, the microbial DNA could also contain identifying information. As a result, in March 2012, Lita Proctor, Coordinator of the HMP, sent an email to all HMP-funded researchers indicating that NIH was concerned about the publication of a paper under review with *Nature* on a microbial population study using a combined dataset from the HMP and the MetaHIT cohorts.[47] One of the findings of the study was that bacterial strain DNA variation in the microbiome data may be identifiable to the individual. The researchers concluded that the identifiability issue was an "incidental outcome" of the study, not "the main focus of the study and that much more extensive sampling and analysis was needed to verify or refute this early result."[48] However, the possibility of identification concerned NIH enough to consider, as a precautionary measure, removing the healthy cohort microbiome sequence data from publicly available databases until the issue could be appropriately analyzed. Subsequently, NIH leadership decided not to take the data off the website, concluding that:

> maintaining the metagenomic microbial community sequence data in open-access databases does not appreciably increase the risks to study participants at this time given that identifying an individual using his or her metagenomic profile would

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> require a source of microbiome sequence data that is connected with identifying information along with considerable skill in cross-matching de-identified sequence data with identifiable data.[49]

In sum, the issues raised by the HMP are not wholly distinctive, but rather add to the body of ethical, legal, and social issues first discussed in connection with the HGP. The fact that the microbiome may be able to tell us about someone's current or past behavior is perhaps the most unique feature of microbiome research. While our microorganisms may tell us something about our individual behaviors that our genes do not, this issue arguably falls under the umbrella of stigmatizing factors also identified by the HGP. As such, the challenges posed by the HMP add depth to some of the problems with the Common Rule identified by the HGP and raise questions about whether additional measures (in the Common Rule, guidance documents, or other laws, such as GINA) may be required to protect data collected by microbiome researchers and how to inform subjects about the potential risks of disclosure of this data.

Implications of Ethical Issues in HMP for Research on Human Subjects

The ANPRM, in part, recognizes the need to be responsive to new large-scale biomedical research, such as the HGP and the HMP, as illustrated by its focus on research that is conducted at multiple sites, that raises more issues of confidentiality and data security, and of modifications to informed consent to reflect future uses of biospecimens. In this section, we explore certain proposed changes to the Common Rule that illuminate ethical issues in the type of human subjects research undertaken by large-scale, population-based initiatives such as the HGP and HMP. We do not attempt to list every proposed change suggested by the ANPRM, but rather address those proposed changes that are most relevant to HMP research. We conclude that the Common Rule, for the most part, is robust enough to accommodate the ethical issues posed by the HMP and that rather than making a number of proposed changes to the Rule itself, more attention be given to how the Rule is applied, and more assistance be provided to IRBs that are responsible for interpreting and implementing the Rule. These conclusions are limited to the specific issues we examine below. The HMP also raises a number of issues that are relevant to other types of research. These include consent for future use of biospecimens, biobanking, and ownership of biospecimens. Because these issues are the subject of intense debate and discussion across many other types of research they are not addressed in this paper.

Facilitation of Multisite Review

The proposed changes to the Common Rule discussed in the ANPRM include streamlining IRB review of multisite studies and potentially mandating that "all domestic sites in a multisite study rely upon a single IRB as their IRB of record for that study."[50] This appears to mean that local IRBs could not insist on approving protocols for research being conducted at their institutions in a multisite study, thus reducing the number of IRBs that have to approve multisite protocols and the time and resources devoted to multiple IRB reviews. Multiple reviews often lead to many changes to the protocol and differing views on what is required for the research. Different IRBs may have different interpretations of the risks and

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benefits involved in a study, the thresholds of acceptable action, and the language required in informed consent forms.

Efforts to facilitate the approval process for multisite studies should benefit ongoing efforts under the HMP to understand the commonalities across the human microbiomes and establish the reference catalogue of our microbial genome. Multisite studies are extremely important for any type of human research that is attempting to establish a comprehensive catalogue of the components of the human body and/or how it functions. These projects require a broadly representative sample of the human species based on such factors as race, ethnicity, gender, age, sexual orientation and sexual practices, diet, socioeconomic background, environmental exposure, disease and disability, geographical location, and medication exposure. As a result, the projects require human subjects from around the world, as well as from urban and rural areas, and from different cultures. While a change in the Common Rule to streamline IRB approval of multisite studies or mandate a single IRB for multisite studies would be a benefit to the HMP and other similar "big science" research studies, it may make more sense to consider the type of research being proposed rather than to mandate this change for all multisite research studies. Additional thought must also be given to how the central IRB would be chosen in order to eliminate the possibility of "forum-shopping." An alternative proposal that may be more acceptable to researchers conducting studies at multiple sites is to create a centralized review process that includes representatives of multiple IRBs or a mechanism for resolution of conflicts when there are both a central and a local IRB.

Improved Consent Forms

The proposed changes to the Common Rule include improving consent forms by "prescribing appropriate content that must be included in consent forms, with greater specificity than is provided in the current regulations" and "making available standardized consent form templates, the use of which could satisfy applicable regulatory provisions."[51] The informed consent template that NHGRI provided to researchers involved in the Healthy Cohort Study and the HMP demonstration projects was helpful, although one demonstration project researcher commented that the concepts and the language of the template were very complex and difficult to translate to the research participants. The template served as a guideline and helped fill the need for common language, yet it allowed researchers conducting the demonstration projects to modify the form as necessary to fit their particular needs. We believe templates are useful as long as they are not mandatory and allow researchers to modify them as appropriate for their research. Templates may also be beneficial to new initiatives with multisite studies.

Finally, templates may be helpful in protecting subjects from overly enthusiastic researchers who may overstate the benefits of participating in a study or what may be learned from the study more broadly. Lewis et al. insist that researchers be careful about how they promote the HMP, "particularly to vulnerable populations who may have high hopes for therapeutic benefits."[52]

An informed consent template is provided on the NIH website for genome research and could be a model for microbiome research.[53] As is the case with the HGP, however, our lack

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of knowledge about the implications of the human microbiome raises issues of informed consent with respect to biobanking, or storing, microbiota samples obtained from research subjects. The fact that one's microbiota is not necessarily stable over time may have particular relevance to consent for future use of biospecimens, which may be used to draw unfounded inferences about an individual's microbiota. Guidance from NIH on whether a blanket consent form for future use of samples is appropriate may be helpful to researchers.

Separation of Informational Risks from Non-Informational Risks

The ANPRM identifies three types of risks related to human subjects research. They include physical, psychological, and informational risks. Informational risks are described as those derived

> from inappropriate use of disclosure of information, which could be harmful to the study subjects or groups.…In general, informational risks are correlated with the nature of the information and the degree of identifiability of the information. The majority of unauthorized disclosures of identifiable health information from investigators occur due to inadequate data security.[54]

The ANPRM seeks to rectify inconsistencies between the Common Rule and HIPAA rules and to address coverage gaps that currently exist for protection of data. It also seeks to standardize data protection rules so that they are not subject to the discretion of individual IRBs that may not have the technical expertise necessary to adequately address data security. As a result, informational and non-informational risks would be dealt with separately. IRBs would not address informational risks[55] but would continue to address psychological and physical risks.

Human microbiome research generally involves a combination of informational and non-informational risks. The non-informational risks, i.e., sampling of microorganisms from various body parts and answering survey questions about behaviors, are generally *de minimis*, although some survey questions may elicit psychological harms, depending on the subject population, and some retrieval of microbiota samples, such as intestinal biopsies, may pose more than minimal risk. In contrast, informational risks associated with disclosure of some of the findings, e.g., sexual behaviors, use of illegal substances, and travel to countries of state-sponsored terrorism, may be significant. The specific risk to subjects participating in HMP research is that they may be identified through disclosure of identifiable information about them. This could include information gained from biospecimens taken from them, coupled with responses to survey questions about their behaviors.

The proposed changes to the Common Rule would establish mandatory standards for "data security and information protection whenever data are collected, generated, stored, or used. The level of protection…would be calibrated to the level of identifiability of the information, which would be based on the standards of identifiability under the HIPAA Privacy Rule."[56] Under the standardized data protection rules, individual IRBs would no longer consider informational risks in calibrating the risks and benefits of the proposed study. Rather, given the standardized data protections that would be put in place, the assumption would be that

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risks of disclosure of identifiable information are *de minimis,* and thus need not be considered in the risk-benefit calculation.

As regards the HMP, however, one might want to consider at least two scenarios where de-identification could fail. If we assume that analysis of a biospecimen obtained from a research protocol can reveal a "unique-to-the-individual distribution of microbiota," and that the presence of certain microorganisms implies illegal drug use or visits to particular countries, then even de-identified samples could be harmful to that individual. An illustration would be someone who donates a specimen that reveals his use of cocaine and a recent trip to Pyongyang; he would be harmed if these facts about him became known to law enforcement. If the microbiome information is made available on a research database but is de-identified, anyone authorized to access the database could readily learn that the "owner" of that microbiome used cocaine and visited Pyongyang. Access to the information harms the owner only if the de-identification fails, which could happen in two ways. First, the "encryption and other steps to prevent access to individually identifying information, which would typically be held by the investigators who first obtained the biospecimen, [could be] too weak."[57] Second, law enforcement or some other entity could already have information about the owner that, when conjoined with the de-identified microbiome information, enables them to identify the owner. This is "highly unlikely as law enforcement agencies don't have fecal specimens or other ways of doing a microbiome comparison between what they already have and what becomes available by the research."[58] If, however, such information did become available to law enforcement agents, "then this risk, which doesn't depend on expertise about the adequacy of technical security measures" ought to be considered by the IRB and possibly included in a consent form.[59]

The effort to separate informational risks from non-informational risks does have some benefits for HMP researchers, but it also presents some challenges. As stated in the ANPRM, the proposal stems from concerns about protection of patient privacy and the view that information not currently identifiable may at some future point become identifiable as a result of new technologies. This may be true for data and biospecimens obtained from the HMP, although, as discussed above, there is some debate about the ability to identify individuals based on their microbiome. Whether or not it will be possible to connect one's identity to one's biospecimens, the ANPRM recommends "categorizing all research involving the primary collection of biospecimens as well as storage and secondary analysis of existing biospecimens as research involving identifiable information."[60] While providing standardized technology-based security protections for data gathered from the HMP will most likely reduce risks associated with disclosure of individual subject information, the ANPRM does not address the risks of group harm or group stigma associated with being classified as a member of a group with stigmatized behaviors or characteristics. These kinds of risks could be the result of new information gained from the HMP, such as the data gathered in the studies of the vaginal and male urethral microbiomes.

> The possibility for group harm or group stigma is a risk for subjects who participate in HMP research. This is largely because one's microbiome is, or can be, associated with one's behaviors or genetic background (including race and ethnicity), some of which may be the basis for unfair treatment or discrimination.

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Separating informational risks from non-informational risks and requiring an IRB to classify research studies based only on non-informational risks also raises questions about what subjects ought to be told during the process of informed consent. Will informational risks associated with storage of sensitive information or group harms be addressed at all in the informed consent form? Given that human microbiome research is a combination of both informational and non-informational risks, it would seem appropriate to inform subjects of the way that informational risks will be addressed.

Expansion of Exemptions from IRB Review — Excused Research

The ANPRM recommends expanding the category of IRB-exempt research to include a new category of research, called excused research. Currently, exempt research includes surveys unless: "(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation."[61] The proposed change would eliminate the language after "unless" so that survey research would be excused from IRB review "regardless of the nature of the information being collected, and regardless of whether data is recorded in such a manner that subjects can be identified."[62] The justification for this change is that the studies would be subject to the new standard data security and information protection standards.

Although the proposed rule changes also would require written general consent for use of pre-existing biospecimens in research, it is not clear how this would apply to HMP research. It appears that in collecting the biospecimens, which would not be exempt from IRB review, researchers would need to obtain consent for subsequent use of the specimens in other research studies. Could subjects provide adequate consent without knowing that those specimens might be matched with responses to survey questions about sensitive activities or conditions? A more protective approach would be not to excuse survey research that includes questions about such behaviors as drug use or other illegal activities, sexual practices, or questions about sensitive medical diagnoses such as HIV or other STIs — questions that may be asked in human microbiome research. This approach should apply even if data security is excellent because of the risk of psychological harm or embarrassment that could result from asking such questions.

Human Subjects Research Issues of Particular Concern for the HMP

Group Stigma

The possibility for group harm or group stigma is a risk for subjects who participate in HMP research. As discussed above, this is largely because one's microbiome is, or can be, associated with one's behaviors or genetic background (including race and ethnicity), some of which may be the basis for unfair treatment or discrimination. For example, an individual who has a gut microbiome associated with smoking or consumption of large quantities of alcohol (even if he does not smoke or consume alcohol) could be subjected to employment or insurance discrimination, even though such actions would technically amount to mislabeling or stereotyping.[63] Or, a woman's vaginal microbiome could be associated with

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having multiple sexual partners or engaging in certain sexual practices (even if she does not engage in these activities), which could be the basis for stereotyping and social ostracizing that may affect her ability to have sexual relationships, to marry, or to have children.

These group harms are not the traditional group harms associated with a pre-identified group, i.e., one that can be easily determined because of the individual's race, ethnicity, or religion. In the context of traditional group harms, "all members of a socially identifiable population may be placed at risk by the identification of genetic features linked with their common identity. Prominent examples are the associations of African-Americans with sickle-cell trait and Ashkenazi Jews with specific *BRCA1* alleles."[64] The type of group harm associated with the HMP, however, may be a more insidious harm — one that is not known to the individual or the researcher prior to participation in the research. This type of group harm or group stigma is not unique to the HMP; it was also identified as a potential risk of the HGP and has been a product of anthropological and sociological research. Both genetics research and microbiome research may bring into existence new types of groups unknown to researchers today that are subject to group harm because of their genotype or microbial type. An example might be a microbiome associated with low fertility. Group harm that results from a particular genotype or microbiome type also affects those who do not participate in the research but who share the relevant stigmatizing genotype or microbiome type with the research subjects.[65] While this type of group harm is important to address in research that may lead to new kinds of groups, the fact that it may not be obvious to outside observers to which group an individual belongs helps mitigate the harms that may come about when a stigmatized group can be easily identified by appearance or behavior.[66]

A major criticism of the HGP was its failure to address group harm and group stigma. IRBs do not generally address group stigma at all because it is not within their jurisdiction to do so. However, there is an NIH policy on "Genome-Wide Association Studies" (GWAS)[67] that asks "institutions submitting GWAS datasets to certify that an Institutional Review Board (IRB)…has considered [risks to identifiable groups].…"[68] The policy goes on to say that "in the event that requests raise questions or concerns related to privacy and confidentiality, risks to populations or groups,…the DACs [NIH Data Access Committees] will consult with other experts as appropriate."[69] Outside of this statement there are no other agency policies or guidance documents on group harm related to genetics research.

Issues of Justice Regarding the Selection of Research Subjects

The HMP, like the HGP, may also implicate issues of justice and equity in the design of research studies and selection of research subjects. The Common Rule states that an IRB must be satisfied that selection of subjects is equitable.[70] Justice, or what is equitable, more specifically deals with whether the burdens and benefits of risks are fairly allocated across research subjects and whether one social group is disproportionately harmed or preferred by the design of the research or by its potential outcomes.

In terms of research design, the HMP "Healthy Cohort study" raises questions as to representativeness of the sample population studied and whether the effort was to include "healthy" subjects or "normal" subjects. This issue is important as it may lead to bias in who benefits from the project. The microbiome literature uses both the terms normal and healthy

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to describe the research subjects. In a 2009 article, the NIH HMP Working Group described the recruitment of subjects to the study stating that "the term 'normal' rather than 'healthy'" was used to reduce the number of exclusionary criteria — "recruitment using a protocol calling for volunteers who were 'healthy,'" they asserted, "would have so many exclusion criteria that recruitment would be very slow or impossible."[71] However, more recent articles have referred to the effort to create a reference catalogue of the human microbiome as the "Healthy Cohort Study,"[72] focusing on "healthy young adults whose core microbiomes were not likely to be perturbed by infectious comorbidities and exogenous exposures."[73] The focus on the "super healthy" evoked some criticism for its over exclusiveness. Relman points out that gum disease, the most common basis for exclusion, is a "condition that is increasingly regarded as 'normal' in developed countries. Hence, one can be normal but not necessarily 'healthy.' Furthermore, the prevalence of overweight and obese individuals and the chronic use of prescription drugs [both exclusion criteria in the study] are becoming more common in this country and others."[74]

HMP researchers who are aware of the studies of the vaginal microbiome have pointed out that conditions referred to as "abnormal" are more likely to be present in minority women, thus potentially excluding them from study participation. The observation brings us back to the question of what is "normal" and who we look at and when we look at them to answer that question. If our selection group is not representative of the broader population, it may lead to developing therapies that ignore certain groups. Lewis et al. point out that given that the reference microbiome is being constructed with samples primarily from Euro-Americans "living in Houston, Texas and St. Louis, Missouri," if a "microbiome-related predisposition for disease is more common to one community or ethnic group than others, then the science may be much more prepared to develop interventions with Euro-Americans of middle to upper socio-economic status than with others."[75] IRBs need to take these factors into consideration when reviewing protocols for population based studies.

Research with Minors

The Common Rule (45 CFR part 46 subpart A) does not address research with minors, but such research is addressed in Subpart D of the federal regulations on human subjects research. Subpart D considers whether the proposed research involves only minimal risk or greater than minimal risk and requires that "adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians." The inclusion of minors — especially adolescents — in microbiome research raises two central questions. First, whether the research involves only a minor increase over minimal risk, and second, whether assent, rather than consent, is sufficient for research involving adolescent subjects.

The regulations state that research on children that involves only a minor increase over minimal risk and no prospect of direct benefit to subjects is permissible as long as the research "presents experiences to subjects that are reasonably commensurate with those inherent in [the subject's] actual or expected medical, dental, psychological, social, or educational situations"; is likely to generate "generalizable knowledge"; and provides "[a]dequate provisions…for soliciting assent of the children and permission of their parents or guardians."[76] For adolescents, there are no clear developmental reasons to restrict the

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content of assent relative to that required for consent. Thus, if the research is determined to represent only minor increases over minimal risk, many of the issues related to microbiome research would require disclosure of the same information to adolescents and adults. Because Subpart D leaves determination of assent to individual IRBs, there are no formal criteria for research assent. Adopting more uniform approaches to informational risks, as envisioned by the ANPRM, could fill this void if IRBs reviewing HMP studies with informational risks begin to require “consent” rather than “assent” of minors. Since the ANPRM does not address assent of minors to informational risks, a shift from assent to consent in this context will require individual IRBs to make determinations that age and maturity render the consent requirements appropriate.

Ultimately, a review of Subpart D as it relates to “big science” research may be in order, especially if it discourages studies of minors. Exclusion of minors from attempts to describe the definitive human microbiome, for example, leaves an enormous gap in understanding how the development of microbiota influence the health of children and adolescents, as well as longer-term influences on adult health. Projects within the subsequent Human Microbiome Demonstration Projects have addressed the microbiota of children and adolescents, but primarily to investigate specific disease conditions. This suggests that research such as the HMP — intended to describe the range and extent of ‘normal’ — should give greater attention to inclusion of minors, especially because of the arbitrary (at least from the perspective of the microbiome) distinction between “child” and “adult” represented by age 18.

Incidental Findings

The Common Rule does not address how researchers should deal with incidental findings in the context of the HMP or other studies. We need to confront what “incidental findings” mean in the context of the HMP and what types of incidental findings researchers should be obligated to disclose to research subjects. Should the disclosure determination be based on clinically significant findings even if the individual is asymptomatic of the condition found? If so, do we know what constitutes clinically significant pathology in terms of our microbiome? An example of this sort of question has arisen in research on the vaginal microbiota and whether women have bacterial vaginosis (BV). The test for BV is quite subjective, and the methodology is nonspecific. Typically, BV is associated with a lack of lactobacillus, yet there are women who would qualify as having BV based on this criteria, even though they are asymptomatic and have been that way over a long period of time.[77] Telling a woman that she has what appears to be BV can also be psychologically devastating and, until we better understand the relationship between the vaginal microbiota and pathology, such information should probably not be disclosed, unless we can associate certain health risks with these types of microbiota.

Researchers studying the urethral microbiome of adolescent males confronted a similar issue in determining how to address incidental findings of STIs. For well-established STIs (for example, chlamydia), the researchers explicitly noted in the informed consent form that subjects would be tested for those STIs, and if discovered, the subject would be notified and treated. However, there are a small number of emerging STIs for which there are no

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consistent recommendations for treatment. These STIs were not addressed in the consent form. Of course, the potential for incidental findings of infectious disease raises the need for disclosure not only to the research subject, but also potentially to public health authorities. Other factors to consider are whether the infectious condition is treatable and whether an individual has a microbiota that predisposes him or her to diseases that can be prevented. The public health implications of information gained from the HMP are perhaps the most distinctive aspect of how incidental findings should be dealt with in this type of research.

> Rather than lock DHHS and researchers into new rules and regulations when flexibility is of utmost importance to address emerging areas of scientific research and technology, it would be better to deal with these issues through guidance documents, templates, or best practices prepared by NIH or the Office of Human Research Protections. These methods would enable researchers and IRBs to address new issues in ways that could be more easily modified than laws or official regulations. Such guidance documents have been used to some extent by NIH and its different Institutes, but there is no official guidance, for example, on returning unanticipated findings or how to address group stigma, either in the evaluation of research or in informed consent forms.

Should the Common Rule Attempt to Address These Issues?

As a final matter, we raise the question whether the Common Rule *should* cover these unaddressed issues. A strong argument can be made that the Common Rule need not be changed to address the issues identified above because the Rule as it now stands has sufficient elasticity to allow researchers to adequately address them. Rather than lock DHHS and researchers into new rules and regulations when flexibility is of utmost importance to address emerging areas of scientific research and technology, it would be better to deal with these issues through guidance documents, templates, or best practices prepared by NIH or the Office of Human Research Protections. These methods would enable researchers and IRBs to address new issues in ways that could be more easily modified than laws or official regulations. Such guidance documents have been used to some extent by NIH and its different Institutes, but there is no official guidance, for example, on returning unanticipated findings or how to address group stigma, either in the evaluation of research or in informed consent forms.

Flexibility is essential when dealing with new areas of research because researchers and regulators will learn important information as they progress in their studies. New knowledge will result in some therapies and/or interventions becoming lower-risk over time, but also may identify new hazards that were previously unknown or underappreciated. Some issues are also extremely difficult to deal with “up front” through new rules or laws. Group stigma is one example. This is especially true when individuals are not identified with a particular group at the start of the research and do not have a known common identity. As a result, they are not in a position to protect themselves as a group. For example, community consultation would not be an adequate response to group stigma resulting from genetic or microbiome research because the “community” at risk would not be self-identifying. Some authors have argued that “[t]o the extent that the risks of stereotyping are serious, they call for regulation

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rather than a consultative process. And since some of the risks of stereotyping and stigma result from prejudice and confusion about the extent to which genetic and social groupings coincide, engagement with groups may be counterproductive."[78] In reaction to research on the HGP, states and Congress passed new laws, such as GINA, to protect research subjects from discrimination by insurers and employers, rather than change the Common Rule. Whether GINA would apply to information gained from microbiome research is still an unanswered question. But even if it did, while such laws are helpful for some types of group harms, they will not work for others. The latter includes social stigma, such as exclusion of individuals from social gatherings or intimate relationships. In such cases, public education campaigns, including such risks in informed consent documents, and/or discussing the risks with potential research subjects may be more appropriate and effective.

Biographies

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References

1. "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators," 76 *Fed. Reg.* 44,512–44,531 (July 26, 2011).
2. *Id.*, at 44,513.
3. Large-Scale Biomedical Science: Exploring Strategies for Future Research. Washington, D.C.: National Academies Press; 2003. National Cancer Policy Board of the Institute of Medicine and Division on Earth and Life Studies of the National Research Council. at 1.
4. *Id.*
5. A third "big science" project, not addressed in this paper, is the "1000 Genomes Project" an international effort begun in 2008 to establish the most detailed catalogue in existence of human genetic variation. See The 1000 Genomes Project Consortium. A Map of Human Genome Variation from Population-Scale Sequencing. Nature. 2010; 467(7319):1061–1073. [last visited April 8, 2013] *available at* <http://www.nature.com/nature/journal/v467/n7319/full/nature09534.html>. [PubMed: 20981092]
6. Stone, M. [last visited April 8, 2013] NIH Builds Substantial Human Microbiome Project. Microbe Magazine. Oct. 2009 *available at* <microbemagazine.org>
7. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The Human Microbiome Project. Nature. 2007; 449(7164):804–810. [PubMed: 17943116]
8. Hawkins AK, O'Doherty KC. 'Who Owns Your Poop?': Insights Regarding the Intersection of Human Microbiome Research and the ELSI Aspects of Biobanking and Related Studies. BMC Medical Genomics. 2011; 4(72) [last visited April 8, 2013] *available at* <http://www.biomedcentral.com/1755-8794/4/72> (citations omitted).
9. See Stone, *supra* note 6.
10. NIH News. [last visited April 8, 2013] NIH Human Microbiome Project Defines Normal Bacterial Makeup of the Body. Jun 13. 2012 *available at* <http://www.genome.gov/27549144>
11. See Stone, *supra* note 6.
12. The NIH HMP Working Group. The NIH Human Microbiome Project. Genome Research. 2009; 19(12):2317–2323. [PubMed: 19819907]
13. See Turnbaugh et al., *supra* note 7, at 804; see also Proctor LM. The Human Microbiome Project in 2011 and Beyond. Cell Host and Microbe. 2011; 10(4):287–291. [PubMed: 22018227]
14. See Kolata G. In Good Health? Thank Your 100 Trillion Bacteria. New York Times. Jun 13.2012
15. Relman DA. Learning about Who We Are. Nature. Jun 14; 2012 486(7402):194–195. 195. [PubMed: 22699602]
16. See NIH Human Microbiome Project – Core Microbiome Sampling Protocol A. Feb 28.2011 last visited April 8, 2013*available at* <http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000228.v3.p1>
17. Aagaard K, et al. The Human Microbiome Project Strategy for Comprehensive Sampling of the Human Microbiome and Why It Matters. FASEB Journal. Mar; 2013 27(3):1012–1022. [PubMed: 23165986]
18. McGuire AL, Achenbaum LS, Whitney SN. Perspectives on Human Microbiome Research Ethics. Journal of Empirical Research on Human Research Ethics. 2012; 7(3):1–14.
19. See Relman, *supra* note 15, at 194.
20. See Stone, *supra* note 6; see also Proctor, *supra* note 13.
21. The complete dataset is available through a Data Analysis and Coordination Center hosted at the University of Maryland School of Medicine. Baltimore MD: <www.hmpdacc.org> [last visited April 8, 2013]
22. See Proctor, *supra* note 13.
23. *Id.*
24. *Id.*
25. Ravel J, et al. Vaginal Microbiome of Reproductive-Age Women. Proceedings of the National Academy of Sciences. May 7; 2010 108(Supp. 1):4680–4687. [last visited April 8, 2013] *available*

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at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3063603/>. Gajer P, et al. The Temporal Dynamics of the Vaginal Microbiota. Science Translational Medicine. 2012; 4(132ra52):1–12.

26. See Ravel et al., *supra* note 25, at 1.
27. *Id.* (citations omitted).
28. *Id.*, at 2.
29. *Id.*, at 4.
30. *Id.*
31. *Id.*, at 5.
32. *Id.*, at 5.
33. See Gajer et al., *supra* note 25.
34. Fortenberry, JD., Nelson, DE., Dong, Q. [last visited April 8, 2013] Marker Paper: The Urethral Microbiome of Adolescent Males. Nature Precedings. 2010. *available at* <http://dx.doi.org/10.1038/npre.2010.5221.1>
35. *Id.*
36. See Nelson DE, Van Der Pol BJ, Dong Q, Mi D, Katz BP, Sodergren E, Weinstock G, Fortenberry JD. Dynamics of Bacterial Communities of the Coronal Sulcus and Distal Urethra of Adolescent Males. PLoS One. 2012; 7(5):e36298. [PubMed: 22606251]
37. See Proctor, *supra* note 13, at 289.
38. See National Human Genome Research Institute. Informed Consent for Genomics Research. last visited April 8, 2013*available at* <http://www.genome.gov/27026588>
39. Lewis CM, et al. The Human Microbiome Project: Lessons from Human Genomics. Trends in Microbiology. Jan; 2012 20(1):1–4. [PubMed: 22112388]
40. See Relman, *supra* note 15, at 195.
41. Bolton D, Niv Y. Ghrelin, Helicobacter pylori and Body Mass: Is There an Association? Israeli Medical Association Journal. 2012; 14(2):130–132.
42. McAuliffe, K. [last visited April 8, 2013] How Your Cat Is Making You Crazy. The Atlantic. Mar. 2012 *available at* <http://www.theatlantic.com/magazine/archive/2012/03/how-your-cat-is-making-you-crazy/308873/>
43. *Id.*
44. See McGuire et al., *supra* note 18, at 7 (citing Fierer N, Lauber CL, Zhou N, McDonald D, Costello EK, Knight R. Forensic Identification Using Skin Bacterial Communities. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:6477–6481. [PubMed: 20231444]
45. See Hawkins and O'Doherty, *supra* note 8, at 3; see also *id.* (Fierer et al.).
46. See McGuire et al., *supra* note 18, at 7.
47. See email from Lita Proctor, Coordinator, Human Microbiome Project, NHGRI, to HMP-funded researchers (March 14, 2012), on file with authors.
48. *Id.*
49. Email from Lita Proctor, Coordinator, Human Microbiome Project, National Human Genome Research Institute, December 5, 2012 (on file with the authors). See also Schloissnig S, Arumugam M, Sunagawa S, Mitreva M, Tap J, Zhu A. Genomic Variation Landscape of the Human Gut Microbiome. Nature. 2013; 493(7430):45–50. [PubMed: 23222524]
50. 76 *Fed. Reg.* 44,512–44,522.
51. 76 *Fed. Reg.* 44,523.
52. See Lewis et al., *supra* note 39.
53. See Informed Consent Elements Tailored to Genomics Research. last visited April 8, 2013*available at* <www.genome.gov/27026589>
54. 76 *Fed. Reg.* 44,516.
55. *Id.*
56. *Id.*
57. Comments of Jack Schwartz on draft of article, October 1, 2012.

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58. *Id.*
59. *Id.*
60. 76 *Fed. Reg.* 44,525.
61. 76 *Fed. Reg.* 44,518.
62. *Id.*
63. The likelihood of such group discrimination is discussed in the context of genetic discrimination. See Juengst ET. Group Identity and Human Diversity: Keeping Biology Straight from Culture. American Journal of Human Genetics. 1998; 63(3):673–677. [PubMed: 9718361] Juengst provides the example of a finding that some particular group carries a relatively greater genetic propensity for alcoholism may be over-interpreted "as universally predictive for the group." *Id.*, at 673. He states that "[t]he resulting stigmatization of members of that group could then be used to deny social goods and opportunities to individuals who might be at no great risk of becoming alcoholics – or even to justify coercive and unnecessary medical treatments." *Id.*
64. Foster MW, et al. The Role of Community Review in Evaluating the Risks of Human Genetic Variation Research. American Journal of Human Genetics. 1999; 64(6):1719–1727. at 1719. [PubMed: 10330360]
65. See Hausman D. Protecting Groups from Genetic Research. Bioethics. 2008; 22(3):157–165. [PubMed: 18257802]
66. See Hausman DM. Group Risks, Risks to Groups, and Group Engagement in Genetics Research. Kennedy Institute of Ethics Journal. 2007; 17(4):351–369. [PubMed: 18363270]
67. A GWAS is "defined as any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition." See 71 *Fed. Reg.* 51,629 (August 30, 2006).
68. "Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)," 72 *Fed. Reg.* 49,290 (August 28, 2007).
69. *Id.*, at 49,292. It is not clear whether this policy would apply to groups that are not identifiable at the start of the research.
70. 76 *Fed. Reg.* 44,517.
71. The NIH HMP Working Group, *supra* note 12.
72. See McGuire et al., *supra* note 18. See also Proctor, *supra* note 12 and Aagaard et al., *supra* note 17.
73. See Aagaard et al., *supra* note 17, at 1014.
74. See Relman, *supra* note 15, at 195.
75. See Lewis et al., *supra* note 39, at 2.
76. 45 CFR 46.406.
77. See Gajer et al., *supra* note 25.
78. See Hausman, *supra* note 65, at 164 (citing Juengst E. Group Identity and Human Diversity: Keeping Biology Straight from Culture. American Journal of Human Genetics. 1998; 63(3):673–677. [PubMed: 9718361] and Davis DS. Groups, Communities, and Contested Identities in Genetic Research. Hastings Center Report. 2000; 30(6):38–45. [PubMed: 11475994]

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Table 1

Vaginal pH and Ethnicity (Adapted from Ravel et al.)

Race/Ethnicity	White & Asian	Black & Hispanic
pH	<4.5	>4.5