U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

# SECRETARY'S ADVISORY COMMITTEE ON GENETICS, HEALTH, AND SOCIETY

Eighth Meeting

Thursday,
October 19, 2005

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P R O C E E D I N G S (8:38 a.m.)

MS. BERRY: Good morning. Welcome to the eighth meeting of the Secretary's Advisory Committee on Genetics, Health, and Society. You might be wondering who this imposter is. I'm not Reed Tuckson, and I don't even play him on TV. I'm Cindy Berry, and I'll be serving as acting SACGHS Chair for this meeting. Dr. Tuckson had a family emergency and couldn't be here today with us.

We typically begin our meetings with introductory remarks from the Chair. We're going to do something different today. We've modified the format slightly so that we can move very quickly into today's session on large population studies. I'll review the rest of the agenda and provide a few updates later this morning, but first I do want to point out that the public was made aware of this meeting through notices in the Federal Register, as well as the SACGHS website and listserv.

I'd like to welcome members of the public in attendance, as well as viewers tuning in through the Web cast. Thank you very much for your interest in our work.

I should point out, too, that on this day in history, in 1812, Napoleon began his disastrous retreat from Moscow. It's a very important date. Our general this morning will be Dr. Huntington Willard, Chair of our Large Population Studies Task Force. He will introduce today's session and review the task force's work since our June meeting, and I'm confident that under his leadership we will have a much better fate than Napoleon's Grand Army.

So with that, I turn to Hunt.

DR. WILLARD: Thank you, Cindy, and good morning. I've been accused of many things. Having a Napoleon complex is not one of them.

(Laughter.)

DR. WILLARD: Nonetheless, here I am.

I want to briefly this morning, before we get into the major session, to review what the Large Population Studies Task Force has been up to and introduce the session today before we hear from our guests.

First to begin and refresh your memory, especially to refresh the memory of those who are on the task force, this is the list of its members. We've convened several times over conference calls with a variety of assigned duties in order to get where we are today, and I thank all the members of the task force, both those who are members of SACGHS and the ex officios.

The issue that was handed to us was to explore the issue of large population studies as one approach to learn more about the relationship among genes, environment and common disease, where the goals of those studies are principally to move towards improvement of health in this country with intermediate steps along the way of determining the mechanisms underlying common and complex disease, and ultimately informing, we hope, treatment and prevention strategies.

What I would like to do in the next 20 minutes is to review the steps this full committee took in assigning the task force, go through the task force's review of a very helpful document that was prepared by an NIH work group, a very comprehensive report that was made available to the public just about the time of our last meeting in June, and then provide an overview for today's session.

So the background is that we were requested back in the very beginning,

some two-plus years ago, to weigh in on the value of a large population study in this country. Through our priority-setting process a year and a half ago, we decided that this topic did indeed warrant in-depth study. In October 2004, a year ago now, we formed the task force to guide the committee and to explore the different issues that would need to be tackled, and in the February/March meeting that we had, we spent a full day hearing from presentations that provided us with a number of facts about the nature of large population studies, and specifically looked at some existing projects both within this country and outside of this country in order to give us a sense of what some of the issues would be or could be that would come to the fore.

As part of that, that session ended up facilitating a discussion of a variety of both scientific as well as ethical, legal and social issues around such studies, and we decided at the end of that meeting that the next step would be to develop a report, and today's session is one step along the way towards that report.

The goal would be to identify the key policy issues around a potential large population study mounted in this country and to have the report outline mechanisms that could be used to address the identified issues, and thereby hopefully help the Secretary in his deliberations about exactly how to proceed.

I should say that we were in touch with Dr. Zerhouni's office and this general strategy was endorsed by him and his staff in that we were not going to look specifically, and we won't today look specifically at the scientific issues that underlie a large population study but rather tackle larger and broader policy and process issues that would need to be tackled in any event, regardless of the scientific issues.

So the major action items from our June meeting for the task force were that the task force would review the work group report that came from the NIH and provide an update this morning, which I will do; and then that we would coordinate a meeting to gather input from the scientific and ethics communities, as well as the public at large. However, the task force decided that it really wasn't in our purview or in our particular area of expertise to move towards an in-depth public engagement on this issue, but rather that what we should do is provide the Secretary with our advice about essentially what the best practices were in the area of public engagement and then allow him to decide what the right mechanism and who the right group or groups might be who would engage the public in their support and/or concerns about the nature of a large population study such as this.

So first let me kick off with a review of the work group report. The NIH brought the work group report to our attention at their meeting in March of 2005, although the report wasn't available at that time, and became available just prior to our June meeting. We thought that this report, which is exceedingly comprehensive and was assembled largely through the efforts of NHGRI, with representation from a variety of experts, a very impressive list of experts from around the country, that the best thing that we could do would be to review it as a task force and then present to you, the full committee, our sense of what that task force was all about.

As part of this, I want to bring your attention to a background paper that was prepared by staff that's located in Tab 4 of your briefing books, and this presents the full report of the work group and many of the specific findings that our task force pulled out from that. I'll summarize the highlights here, but our full sense of our review is found in Tab 4.

I believe also in Tab 4 or somewhere in our briefing book is a copy of an article that Francis Collins published in Nature entitled "The Case for a U.S. Prospective Cohort

Study of Genes and the Environment," which was very helpful to us, as well as to the scientific community at large, and should be considered part of the record from that perspective.

So I want to review the goals of a potential study as outlined in the work group report, look at the key characteristics of a potential study as outlined in that report, and then examine the key policy issues that were highlighted in that report as well. I will say that there were a number of issues that were raised in the working group report on the policy front. Our task force pulled out the ones that we thought this committee could prioritize, and so I'm not meaning to suggest that everything I mention is everything that was in the original work group report. It was actually a very comprehensive analysis, and we're picking out the ones that we thought were most salient to our efforts here.

So the work group was established to examine the scientific basis for a large population study and examine some of the logistical outlines of such a study, extensive power calculations on what might be gleaned from such a study, the number of individuals who would need to be enrolled in such a study, and what we might expect given the known incidence of different common diseases that are found in our population, and exactly what we might find out from such an analysis. As I mentioned before, this involved a significant cohort of national experts in a variety of fields in genetics, genomics, epidemiology and medicine.

So the goals as put forward in the work group report, the goals of a large population study in this country would be to ascertain and quantify all of the major environmental and genetic causes of common illnesses in this country, and to set a stage for hopefully a future of preventive medicine and personalized health care, and ultimately more effective therapy to address and/or prevent the onset of symptoms in many of these common disorders.

What that study revealed was that probably this would take on the order of half a million to a million participants in a prospective manner in order to look for the development of specific clinical endpoints along the way. This half million to a million participants would need to be sampled from a number of different Census tracts and inevitably would require door to door recruitment over a four-year period.

There was a significant examination of, for example, how and why it would be necessary to oversample individuals from underrepresented minority groups in order to make sure that they were, in fact, well represented in a cohort of this size in order to provide the same level of power for detecting significant trends in minority populations as in majority populations.

The data collection at entry for this half million to a million participants would necessarily include a wide breadth of phenotypes and environmental factors, and of course one can imagine that the largest scientific issue is trying to decide exactly what that list is of the phenotypes that one would wish to collect information on, and the environmental factors one would wish to collect information on in order to then predict outcomes as one goes along.

Necessarily, having started the process, you can't decide three years into the study that I wish we had started collecting information on another phenotype. So the critical step comes at the beginning of such a study.

Yet, all of this has to be balanced versus the expected cost of the project, the potential burden on the individual participants and how much they're willing to tolerate in terms of questions and examinations, and the power calculations of what you actually predict that

you'll be able to gain by collecting this information. The conclusion of the work group was that a core group of baseline variables would be collected in all or nearly all of the participants.

Disease outcomes over the course of the study would be assessed using hospital records and outpatient records, as well as other data sources as collected by CMS.

Now, there were a number of key policy issues addressed, and as I said these are the most salient issues that our task force pulled out from the larger working group list, and not the least by any means of which is the nature of public engagement, that a project like this at any magnitude would necessarily require that the public not only be well informed of what the nature of the large population study was to be, but that they also be fully engaged in this and fully supportive of it and feel some sense of engagement and pride in participating in this kind of a project. These same issues have been tackled by other countries that have mounted their own large population studies, some with greater success than others, and that's an issue that in part we want to look at today in terms of the kinds of processes that might be necessary in order to achieve a level of high public engagement.

Another key policy issue concerns the representativeness of the cohort. How do you in a society such as ours, which is exceedingly heterogeneous, how do you begin to determine whether you in fact have a representative cohort? Do you oversample certain groups, as I alluded to a moment ago, in order to achieve that, and how do you get that balance? Necessarily, this doesn't stand on its own. It feeds back into the public engagement because each of the groups that you would like to sample from will have its own particular issues. The public itself is not homogeneous any more than their genomes are, and so one will have to evaluate public engagement from the perspective of the individual population groups that are being brought into this process.

Clearly, there's a need to examine the issue of collaboration both on an international and national scale. There are projects that are already ongoing, even within HHS, as we heard in our meeting back in March. There are other international large population studies, and the question from a process standpoint that needs to be explored is what kind of collaboration one would have in terms of either data sharing or sharing best practices between these different large population studies.

Access to data in terms of privacy, in terms of who has access, how it will be protected, do the individuals ever get the data back becomes a major issue for any project such as this, regardless of scale, but becomes a particular issue for something that's as dramatically large as this one is, and tied to that is the issue of notifying the results that come from this study back to the individuals and the provision of genetic or genomic counseling in order to ensure that the public is well educated about the nature of the data that might emerge from such a study on an ongoing basis, not in your own little clinic but for a half a million to a million people as one goes through it. That was identified by our task force as a major policy issue.

There are intellectual property issues, as there are with all genome and genetically based research, but particularly a key it seems here in terms of the nature of some of the outcomes and discoveries that might come from such a project; confidentiality and privacy; informed consent, which is a broad issue for all kinds of clinical and translational research, but in this case particularly I think takes on an acute sense of urgency.

The task force also identified the concept of a central IRB to manage a project like this, as opposed to a distributed IRB where each institution that might be involved

around the country in trying to collect samples and sign up people into the cohort, that this might be managed much more effectively from a central IRB standpoint, and what are the issues that would be necessary to tackle and solve in getting to that point.

Then we, as everyone does, highlighted the importance of electronic medical records, which is uneven at best in different parts of this country, and yet in this context would need to be brought up to speed in a very significant manner in order to get the best use of the information that one was going to obtain over the course of decades from a half a million to a million enrollees.

So the list of issues that we spent time on came from this review of the working group report from the NIH, as well as the Francis Collins article that I alluded to previously, as well as our own musings and points of view as we discussed in our various conference calls. There's a set, in addition to the policy issues that I've raised here, most of which are on the social and policy end. There's a set of research policy issues as well, some of which we highlighted but most of which were well taken care of by the NIH work group report by itself.

So from this we identified four categories of issues that we thought needed further review and that we as a task force would present this list to the full committee for its consideration today. So let me go through these in kind.

First, broad social issues. Are there data to support the inherent value of such a large population study? Clearly, that's the goal that everyone who considers such a study has, but are there actually data out there that would give us substantial confidence that at the end of the day, or at the end of the decades, that it would be information well worth the effort to emerge from such a study?

Secondly, is a large cohort study the best way to get this information about genetic and environmental influences on common disease, or especially in a heterogeneous population such as we have in this country, and given the nature of some existing cohort studies that are already underway in a variety of different organizations within HHS, are there other ways to approach this issue?

Then lastly, the 900-pound elephant in the corner is the cost of this study. How much will it actually cost, and how does one balance the cost of that study versus other priorities that one has either within HHS in general or within the biomedical research community?

Resource allocation, what tradeoffs would necessarily have to be made if this study were funded. That's always an issue. It's particularly perhaps an acute issue now in the current state of the NIH budget, but nonetheless it's a broad issue that needs to be tackled that we'll need to consider.

Race and genetics, an issue that's been raised before before this committee. Would such a study either increase or decrease the potential stigmatization of individuals belonging to or being assigned to, on the basis of their genome, subgroups of the population, and importantly, would this either reinforce or help dismantle the social constructs of race, and how would one design or consider processes in the design of a large population cohort study that would tip the balance in favor of one or the other of those potential outcomes?

Lastly, from a benefit standpoint, would the benefits of such a study be distributed evenly to all groups within society, or potentially would this exacerbate issues of health disparities rather than address those health disparities?

At the public engagement end, the task force couldn't overemphasize the need for public trust and public engagement and prioritizing the public welfare. How can the public trust, the nature of this kind of project, against a background where their trust of science and genetics in particular, and the government perhaps in particular, is not exactly at an all-time high? How should such a study go about engaging the public both as a single entity and as a number of individual groups, as I alluded to before?

There's also engagement at the level of the scientific community. How can input from the broader scientific community be gathered? The NIH work group obviously engaged a significant number of individuals who contributed to the analysis that was released previously, but there's a much broader scientific community that somehow needs to be heard from in order to either enlist their support or hear their positions on whether such a study is valuable and worth it in the context of resource allocation and the tradeoffs that are necessarily going to need to be addressed across the realm of biomedical research, both basic and translational.

There are a number of access and health care system issues, some of which are issues that this committee has tackled before in terms of their general applicability, but here in the context of a large cohort study, the issues of health disparities, and would the results benefit people who currently have limited access to care, and the issue of diagnosis versus treatment. How will such a project deal with the ethical dilemma that's created by widening a gap potentially between what can be diagnosed or predicted and what the medical community can actually do something about, a gap that already exists now but would potentially or arguably be substantially widened during the course of such a study?

What is the cost burden to the study participants? These are details necessarily of study design, but on the other hand there are process points here that specifically address the public and would necessarily be part of a public engagement process. How will the cost burden affect access to study participation across the different strata of our population?

How should minority communities be accessed? If the uninsured are part of the study, how will they be accessed? Many, again, are details, but details that the task force felt should be brought to the front in terms of the substantial number of policy issues that need to be tackled.

There are also a series of research issues that the task force limited itself to a consideration from research policy perspectives, not the underlying research basis per se of such a project. How would such a new large population study leverage the existing HHS cohorts that are already underway and are, at least in part, addressing many of the same questions? How can that full leveraging be insured? How will collected samples be secured, stored and disposed of? That's a logistical issue that gets to the issue of public trust and to privacy issues but becomes a process issue that needs to be addressed. And the issue of family member notification, which clearly is relevant to all genetic health issues, and always has been, but in this case, with a half million to a million participants, with substantial amounts of genetic and genomic information being collected about them, to what extent would that information be shared with family members beyond that half million to a million, or not, and what would the processes be that would need to be put in place in order to deal with that particular issue?

A detailed recruitment plan would have to be developed. That is both a policy question and a process question, as well as, of course, a specific issue dealing with the research itself. We felt that guidelines needed to be developed for the application of the

research findings and the anticipated technology developments, with particular attention paid to avoiding discrimination and stigmatization as research findings come through over the course of decades.

Necessarily, in a project such as this which would like to look at the interface between the human genome and our environment, we know how to describe the human genome. We're a little less certain about how to actually describe the environment. So from a process standpoint, it's important to determine what the term "environment" means in this context, and how should a variety of environmental, socioeconomic and behavioral variables be measured on one side of the equation to then balance that versus genomic information on the other side of the equation?

We felt it was important to highlight the need for non-coercive recruitment and how protocols for recruitment, enrollment and withdrawal would somehow be kept free of significant incentives that were not somehow coercive or deemed to be coercive by at least some elements of the population. This again is true for all studies but takes on, because of the magnitude of this study, takes on even more importance.

So those were the general policy and social and research policy issues that the task force highlighted, many of which we hope will be informed during today's session and that members of the committee can dig into more deeply, especially in Q&A today. So we thought today's session as we've designed it, the purpose would be to gather input on key policy and process issues and how to address them from various members of both the scientific and the bioethics communities who will be speaking with us today. We also wanted to gather input from experts in the nature of public engagement to share with us their thoughts on what the best practices are and the variety of mechanisms there are in order to engage the public broadly on this or similar issues.

The purpose of the session is to help us inform the report that we decided we would prepare for the Secretary that would identify for him key policy issues around a potential large population study, and to outline some of the mechanisms that could be used to address those policy issues.

It's equally important, I think, what we're not going to do today, and that is we're not assessing the scientific need for such a study, nor are we assessing the specific scientific aspects of the study or the research design, both because those were anticipated in the work group report from the NIH and because that is not in our immediate purview as the Secretary's Advisory Committee. So although we are not going to be making a recommendation on the need for such a study, or necessarily even the best approach to the study design, the committee may want to identify, as the task force already has, identify this as a policy issue, that there is a specific need to address what the need is and what the study design should be for such a study.

So today's session will consist of three different panels that we'll hear from, representing the three constituencies that I alluded to previously. Each panel will be followed by Q&A, and in the science panel each speaker will be followed by Q&A for discussion and questions coming from the committee at large, and then at the end of the day we will have a full committee discussion in order for us to reflect on what we've heard today and to determine our next steps as the committee decides the nature of the report that we would like to prepare for the Secretary.

So that is the end of my comments. Where are we on time with respect to

being over time?

MS. BERRY: Just a little bit over.

DR. WILLARD: So as I said, we're going to hear from initially three distinguished members of the scientific community, and they've been asked to address their perspectives on policy issues surrounding a large population study, and we've asked that they offer us some insights into the best mechanisms and processes for addressing these issues.

We're first going to hear, and we see on the screen, Dr. Gerald Fink via teleconference from MIT in Cambridge. He is a founding member of the Whitehead Institute and is the American Cancer Society Professor of Genetics at MIT. He uses the common baker's yeast to explore critical pathways of cell growth and metabolism. In other words, he's addressing the very issues of gene and environment interactions in yeast that we would need to address in the context of a large population study in human individuals. The applications of his research include cancer research and the development of anti-fungal drugs. He's also intimately familiar with the beginnings of the Human Genome Project and the substantial benefits that the Human Genome Project has brought to the biomedical research community in general, not just those of us who are in the human genetics community.

So, Dr. Fink, welcome.

DR. FINK: I know you can see me. Is there some way we could just pan around so I can see you? You were a blur.

Good morning. I was director of the Whitehead Institute from 1990 to 2001, and I should lay my cards on the table. I'm not, in principle, for or against big science projects or the kind of large population study which you're being asked to evaluate. In fact, I was the director of the institute and responsible for managing a portion of the Human Genome Project that one of my faculty, Dr. Eric Lander, spearheaded here at the Whitehead. In fact, it was a common joke that I was Eric Lander's boss.

I think that the scientific community now is in general agreement, but in retrospect that the Human Genome Project was successful big science, and that Francis Collins was a wonderful leader in this effort. But, you know it wasn't always that way. In fact, if you go back and read about the Human Genome Project at its inception, the scientific community was not completely behind it.

For this reason, I think it's worthwhile to use the beginnings of the Human Genome Project and its ontogeny as a guide to how a new project of the magnitude of the one you're considering might be successful.

So I'm just going to list some things that struck me when I considered this. The Human Genome Project was very focused.

(Videoconference connection lost.)

DR. FINK: Hello? Are we back on?

PARTICIPANTS: Yes.

DR. FINK: Can you hear me now?

PARTICIPANT: Yes, you're live. You're back on. Unmute it. We can't hear you.

DR. FINK: I muted it by accident when we were cut off.

So we need defined benchmarks, and in fact the yeast genome was the first genome. You carried out the genome sequence, but the human genome began with a map of the genome, and then there were successive increases tied to various benchmarks. There was a

defined endpoint, namely the sequence of the entire human genome. There was a defined cost, and I think the interesting thing is that the cost of the study kept going down. That is, the price for every base sequence kept going down rather than going up.

I think this affected what I would say was the scientific community's trust in the project. That is to say, the benchmarks were met, the endpoints were reached, the costs came down rather than going up. So there was originally very great skepticism about this project both in the scientific media and in the public domain, and there was even skepticism I would say about the science and the fate of the R01s, basic research grants. Would this take away from other important science was a question that was booted about by many scientists. But as each tier was completed and the promise realized, the basic scientists became the greatest supporters of the project because it actually added value to basic research. I think that was an extremely important feature, the feedback from the Human Genome Project into the basic research effort.

Where would skepticism arise in the current project? For this, I have to take a slight diversion into some science, but I think it ends up being a policy issue because the science of quantitative trait loci, QTLs, has a long history, and I need to just give you a sense of where I see some concerns about the scientific issues. This is not to say that this is an unsolvable problem, but this is not untrod territory.

What do I mean? Many of the model organisms have been used to try to map complex traits. Perhaps the most well studied area is in the plant field, because the agricultural scientists in this country have tried to breed plants for traits that deal with yield per acre, very complex traits that have to do with productivity and so on, over the years. So this is a very well developed field in the plant field. In the fruit fly field it's also well developed.

I'm going to mention a study in an area that I know best, and that is yeast, and I should say in all the organisms in which these quantitative trait loci have been looked at, and at great resolution, they're all sequenced, all the data is computerized, and there are no ethical issues.

So I'm going to talk about just briefly quantitative traits, associating disease phenotypes with genotypes, because that's ultimately what such a study would like to do. I want to point out that this has been extremely difficult, even in model organisms.

Yeast, as I mentioned, the genome has been sequenced. It only has roughly 6,000 genes. It's possible to have all of the polymorphisms between two strains on a single chip, and there are no ethical concerns about backcrosses. Brothers can be crossed by sisters, brothers by mothers, by grandmothers, et cetera. This is not a big deal in this organism. Those crosses turn out to be extremely important for the resolution not only of simple Mendelian traits but of quantitative traits.

The trait that was looked at very carefully by a terrific scientist was the ability to grow at high temperature. So what you see on the left is a Petri dish, and you can see a Petri dish in which, on the left, a strain that doesn't grow at high temperature and two strains that do. So here the phenotype is very clear, very easy to identify and easy to identify amongst the cohort that one is studying. These research workers wanted to know how many genes were involved in the difference between growth at high temperature and growth at low temperature, and they did a cross and did all sorts of, I must say, extraordinary genotyping at a level that dwarfs anything that could involve a human population because, of course, it's possible to grow billions of yeast, not just millions, and it's possible to look at this.

The best they could do was to map it to 32 kilobases of a chromosome. They tested this by 3,400 markers, and they localized this there, but there weren't just simple differences between these, so they had to resort even to more exotic breeding experiments and genotyping experiments to try to localize actual differences in the genetic code that could account for the heat resistance, and their conclusions of the best study in yeast was that they couldn't find a single difference that was necessary or sufficient for high-temperature growth. They could not find any marker trait association. Furthermore, they concluded that it must have required combinations of common and rare variants to underlie the quantitative traits, and the number of genes that controlled this were far greater than expected.

I went through this brief discussion because I think this system and many others that are model organisms point out how difficult it has been to associate these quantitative trait phenotypes with genotypes. So I don't want to minimize -- it is a policy issue, which is what kind of data will we be able to get, and how can we maximize the possibility of identifying the key genes that are involved in a multigenic disease?

So my sense is that one should follow the experience of the Human Genome Project. I think a pilot study would be the equivalent of the early benchmarks in the Human Genome Project. Experience -- I don't know who said it, but experience lets you recognize the mistake, especially when you make it again. So like the genome project, it seems to me that picking some heritable multigenic disease with a defined benchmark, a target, would gain the confidence that one is going to get statistically significant data. I think this is especially important considering that less than 5 percent of medical records are computerized, whereas all the data that I showed you for yeast and for all these model organisms is easily computerized. The phenotypes are very clear. One would have a defined endpoint, then. One could know what a segment of the project could cost, because I think again, for the scientific community, cost is a big issue.

Finally, what would the government do with the information where the particular variant genes increased the risk of disease a few percent? These are just questions. I certainly don't have answers. Does that mean that that would then be a place to look for cures, collaborations with pharmaceutical companies? Finally, what would be the consequences for the R01s? Would this take away from investigator-initiated research?

I think the project, like the Human Genome Project, would initially be viewed with some alarm because of the scientific issues that I discussed and, of course, the risk to funding. The community would be much more supportive, I think, and reassured if there were proof of principle.

Furthermore, I think a crisp definition of the question. I think the goal as listed in the information I got of understanding the relationships of genes, health and common complex diseases, I don't think that actually works. It seems too general certainly for the scientific community, and I think that a large population study to identify risk factors for a specific disease would gain further trust in the scientific community.

Just in discussing this idea, which is, of course, an idea that was generated from the onset of the Human Genome Project, having discussed this idea with many colleagues, questions that have come up and which I don't have time to discuss, and you obviously have much more time and the expertise to discuss, is the NIH really the right organization? Others have suggested the CDC, pharmaceutical companies. I think this is an interesting question.

Finally, ethical issues. Clearly, I am not an expert in this area, and many of

you are, but my experience is that one can never anticipate the ramifications of genetics studies that inevitably evoke race, gender and age, buzzwords for unanticipated responses. This reinforces my sense that without a successful pilot program, one could, by indirection, create antipathy towards an otherwise laudable goal.

That's the end of my remarks.

DR. WILLARD: Thank you very much for that, Dr. Fink.

Can you hear me, Gerry?

DR. FINK: Slightly. Can you hear me?

DR. WILLARD: More than slightly. That's fine.

We'll open this up to the committee for questions, I think it would be helpful under the circumstances if you would identify yourself when you're asking the question so that Dr. Fink has something more to go on than just a voice.

Julio?

DR. LICINIO: Dr. Fink, in light of the data that you presented with the complex but not so complex trait in yeast, is there any hope to find anything for human disease? That's my question.

DR. FINK: The short answer is yes, but I believe that the nature of human genetics is such that techniques that have worked for plants and worked marginally for yeast will need to be constantly evaluated. These are questions of statistical significance, as one cannot do breeding studies. I was just at a meeting where scientists reported data on a very measurable human trait, high blood pressure, which they successfully identified in small populations genes that affect high blood pressure in those populations, and these were single Mendelian traits. But the attempt to find the multigenic traits responsible for high blood pressure is still an ongoing research project.

So I think the short answer to your question is that I think these techniques can be refined. The question is whether one will be able to find -- if you get too many genes involved in a trait, and it doesn't matter whether it's yeast or humans, then each gene will have such a small effect that, of course, it questions the use of the study. But if there are a small number of genes that affect a trait, then I think, even given our limitations in providing information to the human geneticist, I think that one will be able to extract these data. But I don't think it's going to be easy.

DR. WILLARD: The next question, Emily Winn-Deen.

DR. WINN-DEEN: Thank you for a really very insightful presentation. My question was about pilot studies. It's been brought up that there actually are potentially some existing studies that could be used as "pilot studies," for example the Framingham Study and the Women's Health Study. Do you think it's necessary to initiate new pilot studies, or would a retrospective analysis of what worked and what didn't work in some of these other longitudinal population studies be sufficient?

DR. FINK: I have some familiarity with the Framingham Study. There's a former student of mine who is now the head of the Human Genetics Department at Boston University and is involved in looking at high blood pressure in the Framingham data.

The reason for initiating a new study -- and I don't have the breadth of information to know all the pilot studies that are going on. My visceral response to that is that the Human Genome Project has added a dimension, a new dimension chronologically that makes some of the earlier studies that didn't collect information in the way that would be

important to make statistical differences or don't even have the material, we'd make a new study mandated. Again, I don't know all the pilot studies that are going on, but certainly this is a criticism of some of the earlier studies, that some of the material, either the material or the family histories were not adequate to provide the kind of information that would enable a study like this.

DR. WILLARD: Next question, Robinsue, and Robinsue, you might identify the nature of who you're representing for his benefit.

DR. FROHBOESE: Sure.

Good morning. Robinsue Frohboese with the Office of Civil Rights at HHS.

Dr. Fink, at the conclusion of your remarks, you briefly mentioned the ethical issues of race, gender, age, and I know that some speakers later on today will be addressing these issues in greater depth, but I wondered if you could share with us a little bit more about your insights in this area and the ethical issues that you perceive.

DR. FINK: I have to admit I'm somewhat naive about these ethical issues. I don't mean to sound simpleminded, but I think that scientists are not always in control of the information, and that information clearly can be used by the press and by anyone for their purposes. I remember when there was testing for sickle cell anemia. It was at the time I was at Cornell University. There was testing for sickle cell anemia, and George Foreman, I believe, was on the front page of a newspaper bringing African American children for testing for sickle cell anemia. He was an advocate of it. But the atmosphere quickly changed from being a positive public health measure to a negative one.

I certainly did not anticipate this. So I think it's these unanticipated aspects that you get to anticipate from a pilot study. You can't know them in advance.

DR. WILLARD: I think we have time for two more questions. First, Francis.

DR. COLLINS: Hi, Gerry. This is Francis Collins. I appreciate your thoughtful comments on this. It's certainly true that there are many issues that ought to be considered before undertaking a project on the scale of this, and the reference to the Human Genome Project and all of the planning and specific identification of milestones is well taken.

In terms of your proposal for a pilot project, I think we're blurring a little bit here between two kinds of study designs. There is basically the case/control study design, which is the sort of pilot I think I hear you asking for, where you have affected and unaffected individuals or you have a group on which you've measured a quantitative trait, the kind of study which is going on all over the place now, particularly with the HapMap having come forward now and made it possible for people to do whole-genome association studies as opposed to pedigree-based linkage approaches, which we know have been rather underpowered when it comes to quantitative traits and polygenic conditions, and I would say that kind of pilot not only is getting underway but has even succeeded in some instances, and I would point to the dramatic example of age-related macular degeneration, the most common cause of blindness in the elderly.

Here's a disease which is very late onset where the evidence for heritability was perhaps a little spotty, and yet we now have not one but two loci identified in the course of the last six months. One of them contributes about half of the attributable risk of that disease from a single variant and complement factor H. So at least for that one example, what we

thought might be a very complicated situation turns out to be simpler than anyone expected, with a couple of different loci contributing a very significant part of the risk, not to say that that will happen all over the place.

You can look at type 2 diabetes, where a lot of people have been doing case/control studies based upon linkage analysis, but now increasingly on genome-wide association, and I think everybody would agree that we do have three variants for type 2 diabetes that hold up in multiple studies. They don't contribute a huge amount of the attributable risk, but they do point you towards potential drug targets that could be very valuable to follow up on.

In the quantitative trait arena, I have seen data on long QT syndrome that is probably going to be presented next week at ASHG that suggests that it is possible to prove the principle that you're asking us to look at for a very quantitative kind of trait. This is not people with long QT syndrome. This is just people who are normal in the population who have had EKGs where the QT interval has been measured, and that's been assessed by looking across the genome, again with a HapMap-based approach and association studies, and identified what appeared to be quite impressive evidence of loci involved.

So taking all of your points about how hard this has been in yeast, maybe this time the proper study of humans will turn out to be humans, and we're a better model organism for ourselves than we realized, and the advantages of working with a newly arrived population like Homo sapiens, because we are so much alike, will make this kind of study more tractable than expected.

Again, I just wanted to challenge a little bit this argument that we need to carry out this sort of pilot project on case/control studies as if it wasn't happening, because it is happening all over the place, and I think you can see already signs of pretty good evidence of success. But what the population cohort study has is a really different kind of idea in mind. It is, frankly, not so much designed to do discovery of variants that are involved in quantitative traits for diseases. I think a lot of that will come out of case/control studies. It's really designed to quantitate exactly what does a variant contribute to risk, because case/control studies will always be a little biased in that regard, and most especially to assess gene/environment interactions, which are very difficult to do with case/control studies because you often have a recall bias problem.

So maybe several of these issues could be talked about during the course of today, because I think they're important to keep somewhat separate in our minds. Again, I guess I think maybe it's a little optimistic, but I think we can assume that in the course of the next couple of years, because of the tools that are available and the decreased costs of being able to do really prodigious amounts of genotyping, that the case/control arena is going to provide the kind of pilots that you're interested in. To undertake a U.S. population cohort study is going to take at least a year or two of planning. So don't worry, that pilot data I think will undoubtedly be in hand in considerable amounts long before one would consider enrolling the first subject in a prospective cohort kind of design.

DR. WILLARD: I don't hear a response, so I'm going to move to the next question, the last question. Muin Khoury.

DR. KHOURY: Yes, Dr. Fink, this is Muin Khoury from the Centers for Disease Control and Prevention. I heard you mention in passing CDC, and I wanted to pick up on a couple of threads about the major differences between the Human Genome Project and the

large population cohort.

It's obvious from your discussion and from what has happened in science that the Human Genome Project was designed with very specific endpoints that were met, under budget, and in shorter amounts of time. Here we are embarking on something more open-ended that is not clear how long and how costly it will be, regardless of what the scientific merits are.

You mentioned an early yardstick of success, benchmarks of success in such an endeavor, and I wanted to ask you what you might think as we plan ahead or plow ahead in this regard, what could be some benchmarks in this endeavor. Before you answer, I just wanted to insert my public health perspective because there is a lot of data collection that public health agencies do, like birth defect surveillance systems and cancer surveillance systems and population surveys like NHANES, that are open-ended, and we collect information on large amounts of people, and nobody says at the end of the day you've succeeded or you've failed, because the endpoint is a bit different. We're not trying to test a scientific hypothesis but we're trying to develop a resource by which we can quantify how many people are affected with a certain disease and what's the relationship between different parameters in the general population.

So I don't know if that kind of feeds into your idea when you mentioned CDC or not. But anyway, can you elaborate on what you think are parameters of early success? With the Human Genome Project, when things moved forward, they were under-budget, there were some benchmarks. What could be some benchmarks in this endeavor that could galvanize the scientific community and get them to buy in rather than be scared by such an endeavor?

DR. FINK: I think that's a question for Francis. I mean, I could think of some, but I don't know what he would consider a benchmark for success.

DR. WILLARD: I think we're asking you, Gerry.

DR. FINK: I see.

DR. KHOURY: What do you think Francis should think?

(Laughter.)

DR. FINK: I could imagine some. I mean, it seems to me that in the case of spina bifida, for example, if it turned out that one found that there were in the population people who were particularly deficient in folic acid, it would be very useful to have the kind of information (inaudible) people to a vitamin deficiency, for example, just to take off on your CDC study, which in some ways is open-ended because you can't really identify subpopulations who are specifically at risk, but with these data you could.

DR. WILLARD: Well, with that, and in the interest of time, Dr. Fink, I want to thank you for your time this morning and for sharing your insights with us, and particularly appreciate your doing it as you're marching off to teach a class of MIT students. But thank you very much.

DR. FINK: Thank you all.

DR. WILLARD: With that, and thanking everyone for their patience with the nature of that connection, our next speaker is Dr. Sharon Kardia. She's an associate professor of epidemiology at the University of Michigan at Ann Arbor, director of the Public Health Genetics Program there, and co-director of the Michigan Center for Genomics and Public Health. She is particularly interested in gene/environment, gene/gene interactions, and in modeling complex relationships between genetic variation, environmental variation, and the risk of common and chronic diseases.

Dr. Kardia?

DR. KARDIA: Let me start by thanking the committee for inviting me and perhaps giving you a little bit more information on my background. I'm a human geneticist and statistician by training and study epidemiologically a number of diseases, including cardiovascular disease, hypertension, I've done some diabetes work, worked on the genetics of drug response, and nicotine dependence. I'm also currently a member of two National Academy of Science committees, one on toxicogenomics and the other on assessing social, behavioral and genetic interactions.

It's from these experiences that I have been accumulating a relatively broad understanding for a genetic epidemiologist about the social issues and the policy issues surrounding genetics research and its implications. From my point of view, a large population study of genetic and environmental factors has a lot of advantages and a lot of disadvantages. Although it's probably to my personal scientific benefit that such a study go on, right now I feel like the disadvantages outweigh the advantages.

Right now there are a number of critical social and regulatory policy issues that make the project, in my opinion, premature. For example, the current lack of genetic literacy in the public and health professional arenas make true informed consent for this type of research a major issue. If people don't understand the basic genetic consequences of this information, how are they supposed to properly consent for it? In addition, the lack of a federal genetic anti-discrimination law makes it a liability for the public to participate.

With such a big study involving hundreds of investigators and clinicians, the public is going to be concerned to the extent with which real privacy and confidentiality can be maintained. There is already a lot of fear on the part of the public as to what researchers, doctors, insurance companies, employers and government agencies will do with biobanks and genetic information. My current experiences reaching out to our Detroit Urban Research Center to do community-based participatory research have been, well, an eye-opener. I can hardly get my foot in the door. They don't really want to talk about doing genetics research because of what they perceive as information being out of their control, researchers playing God, and it's been an eye-opener.

There's also a lot of fear by the public health practice community that genetics research will increase health disparities and reduce access to care. For example, we already have instances where smokers are denied access to certain types of care. What if smoking is found to be genetic? What does that do to the way we think about current policies?

In addition, given the power of genetic information, there are serious concerns about having well justified and executed policies about the duty to warn research subjects and their families of the research results. I raise this point because much health education and health behavior research has demonstrated that the public struggles with genetic risk communication and genetic concepts. They often don't retain genetic concepts after a session, and they misinterpret what has been very well crafted to be a precise genetic risk communication.

Many don't even know where their genes are located or why a genetic test might be predictive. For example, studies have shown that subjects receiving genetic information on early-onset colorectal cancer may ignore their negative results -- so these are people who do not carry their familial mutation -- and continue to get yearly screening, because the blood test is not relevant in their minds compared to the clinical examination of where the

disease lies in their colons. So the disconnect, the basic public understanding is going to be a major barrier to any kind of communication.

This kind of misrepresentation does not just reside in the lay public but also with professionals, and that includes people at the policymaking level. In addition, given that most genetics research is still focused on identifying single causative factors and has not matured to complex models of genetic causation, this means that scientists themselves end up promoting a naive biological, deterministic interpretation of complex disorders. This is likely to lead to further misinterpretation and misuse of these genetic explanations in public policy, in courts, in health and life insurance policies, as well as medical practices.

The Burlington Northern Santa Fe Railroad decision to secretly test workers for a mutation associated with carpal tunnel syndrome is just one example of how this type of information could be misused. In this case, it appears that the company wanted to avoid financial responsibility for providing workmen's compensation for their workers' on-the-job injuries.

In general, I don't think we have the necessary experience, infrastructure or scientific culture in which to responsibly carry out a large and important study like this. Genetic science of common complex diseases is simply not mature enough. We're still using the single-gene paradigm of the last century, and we don't understand the real roots of why the genetic factors we are identifying as being significant in one study are not replicating in another.

This is going to be especially relevant for a large population study, because there will be a desire to use all that power of that sample size to highlight definitive findings and statements that, by and large, might be overall a result for the population but do not reflect the local heterogeneity of the genetic/environmental factors where the actual clinical utility will matter in its applications.

Another major issue for me as a scientist is that most geneticists are not well versed enough in the social, behavioral and environmental causes of disease. True interdisciplinary research that integrates knowledge across the levels, from the influence of the genome to the influence of our human ecology, are just now getting started, and currently the two ends of the spectrums, the geneticists and the social behaviorists, are pitted against each other at the funding tables and in institutions. My own experience being a part of our school's Robert Wood Johnson Health and Society Scholars Program has shown me the genuine lack of respect that genetics commands compared to health effects of poverty, racism and unfair social practices. Through a lot of hard work, we are just now sitting down at the table and trying to work from the bottom up and the top down to learn each other's languages and methodologies.

It is clear that we need new models, systems models as an example, and models that incorporate a person's lifetime of exposure to adequately understand genetic influences on health and disease. In this arena, geneticists are appropriately criticized for our simplistic genocentric analyses, our lack of key social behavioral measurements, the lack of replicable results, and the lack of clear causative mechanisms. It's incredibly difficult in many cases to move from a statistical genetic association to an understanding of the mechanism of action that would suggest new therapies, prevention, and that would withstand evidence-based regulatory decisionmaking.

The last point troubles me the most because it means that genetic findings in complex disorders, especially gene/environment interactions, are not likely to pass the muster

that would allow regulatory bodies to create policies to protect people. Although there has been some progress lately in the field of gene/environment interactions, namely people are starting to look at them, such as in toxicogenomic and pharmacogenomic research, the results themselves have exposed immense complexity in integrating this type of knowledge into existing policy standards and methods.

Traditionally, public health policy has focused on the population-level solutions, the one size fits all model, for example, the ubiquitous anti-smoking campaigns. Nobody would disagree with that as a population public health effort. In contrast, genetic information is individual based, family based, ethnic group based, and will require intense research on the implications of specialized policies and regulations for the protection of vulnerable populations.

What if we found that some people are sensitive to their environments and others are not? Is it the responsibility of the individual to take themselves out of harm's way when the rest of society can ignore their vulnerability?

Barbara Koenig's group's paper on looking at smoking through the neurogenetic prism highlights many of the unintended stigmatization, discrimination and ethical issues that come with a difference in sensitivity to environmental factors.

The current risk assessment paradigm in the EPA and the FDA are other examples of issues that are going to arise as we get more genetic information. How are they going to set standards and guidelines for businesses and products based on complex susceptible genetic subgroups? One of the other key issues merging the science, then, with the policy is that for every disease, there's likely to be a different combination of genetic factors. So even defining a vulnerable subgroup or a susceptible subgroup could end up being a nightmare in and of itself, especially when we overlay those genetic definitions with already existing definitions of vulnerable populations based on age, race and disability.

In addition, to my knowledge, the regulatory agencies such as the FDA, the EPC and the Federal Trade Commission, do not have the resources to tackle an upheaval in their systems, and they often do not have enough staff that really understand genetics and genomics. This is slowly changing, but again, it's slowly, and I worry that moving the science along in our particular culture, looking at genetic associations when our regulatory bodies aren't ready for it, would be a mistake.

An example of that that is already playing out is the current lack of oversight on genetic information, genetic testing, and the lack of public education, which leaves the public vulnerable. Genetic testing companies can market directly to consumers, they can market directly to doctors without any regulations at this point. There's no need for them to disclose the real utility or the makeup of their products. We haven't pushed any truth in advertising for genetic testing companies at this point, and guess what's happening? The American market system is working, and Best Buy has recently released a nutrigenomics DNA testing kit. To the best of my scientific knowledge, there's not enough real evidence that would warrant such a direct-to-the-public testing kit.

But the alternative is people are excited by knowing genetics information. The Human Genome Project has done a great job for moving genetics into the public eye, and daily newspaper articles that are trying to show the public what genetic findings are out there are, in a sense, a mixed blessing. Because of their basic paradigm of reporting the news you can use, they tend to overstate the research findings, and this leads to a whole cycle within our

society of aggrandizing simple genetic solutions to complex problems.

One of the questions that the committee asked me to address was how much consultation was needed within the broader scientific community to inform a decision about undertaking a U.S. population study. I have to admit some skepticism here on my part as a researcher. I think asking for the scientific community to comment will lead to a biased sample of very outspoken antagonists from the social epidemiology field who are worried about the geneticization of disease and the excessive use of resources by geneticists. It will also lead to the outspoken proponents who want to be a part of such a large funding -- i.e., revenue -- source for their own operations. When the National Childhood Study started to create working groups to formulate plans for their large population study, I was asked to be on the Gene/Environment Working Group and participated for about a year before getting fed up with the obvious and, I would say, natural self-serving interests of the committee members.

Another key question that you asked is is there general awareness among scientists of the potential of a U.S. large population study. In my experience, the answer is a definite yes, and again it is with some skepticism. Many of the genetic epidemiologists I know think that there is merit to the idea but that this mega-science model will fund a few insiders very, very well and not leave much for the rest of the scientific community. It also won't build on the years and years of experience of doing epidemiological studies, and especially utilizing what genetic epidemiologists have already accrued in terms of cohort studies such as the ERIC Study, the Cardia Study, the Framingham Study, and those experiences, which have taken a huge amount of work to collect information on people and collect it well, makes many of us think that the 500,000 or 1 million person goal is an unrealistically large and broad target to accomplish in a high-quality manner.

I've been fortunate to be a part of NHLBI's Family Blood Pressure Program over the last 10 years that's collected 13,000 individuals and five racial and ethnic groups through over a dozen field centers. It takes a tremendous amount of effort to agree on what should be measured, and how, and then how to package the results. Science is not value-free and neutral. We have a long way to go in terms of learning how to collaborate together and to use existing resources at hand, and this goes not just for the genetics to social epidemiology bridge but among geneticists. We are often competitive, and we also have very strong opinions about what is right and what is not right.

I think you can see from my comments that I just don't think we've had enough time and resources to build the necessary experience or infrastructure to support this kind of ambitious project right now. Maybe in five or ten years it would be an appropriate thing. I think there are a lot of intermediate steps that can be taken along the way. Just getting genetics researchers to work together so that they can use already existing cohorts that can be used to confirm and reject claims of genetic associations would be a major step. Getting genetic researchers to work with social and behavioral epidemiologists and researchers would be a major step.

Another thing which we have not typically done in genetics research is engage the resources of departments of health. There are cancer registries, early death registries, environmental health registries that could be used as a first wave of research. We're trying to do that right now in Michigan, and there are big gaps that expose even more issues.

As the state holders of these registries and the knowledge about the key environmental factors influencing the public's health, it's amazing to me that we have not

involved them in this kind of effort. They have important roles not only as resources but from a policy perspective. Departments of health need to be more prepared for dealing with the genetic information on common disorders and to have working staff investigating the implications of state-level policies on things like informed consent, and setting up mechanisms to handle the public's need for genetic services, like counseling.

In Michigan, we recently had a case where a doctor did a diagnostic genetic test prompted by what we think is a direct-to-doctor advertising campaign by a company, and he did not tell the individual that he was doing the genetic test. He then called up the individual, gave the person the results over the phone, and said there was nothing he could do, this person had a genetic disorder that was basically going to ruin his life, and hung up. This family then contacted the department of health, who tried to figure out whether or not there was anything on the books in terms of what the doctor had done wrong.

The family was left very devastated, and according to Michigan's laws right now, the doctor was under no duty to provide an informed consent or counseling. So this provides an example of things that can happen. We're lucky in Michigan that we have one of the most genetically progressive departments of health in the nation, and still they were left scrambling trying to figure out what to do for this family, who now faced the real possibility of employment discrimination, as well as health and life insurance discrimination.

To end, I think that one of the things that really needs to be done if we're going to use genetics in this country is to invest in the infrastructure, and that means the EPA has got to be ready, the FDA has got to be ready, the FTC has got to be ready, state departments of health have got to be ready, and the public has got to be ready. The last thing we want to do is repeat the sickle cell screening debacle in the '70s, where well intentioned legislatures passed marriage laws to protect people.

Given the right social investment and the investment in new policy systems, I would be greatly enthusiastic about this project. This is my field. I would love to have access to 500,000 people and their genetic information. I just don't think the timing is right, not right now. Thank you.

DR. WILLARD: Thank you, Dr. Kardia, for your forthright comments.

We have time for a few questions from the committee, and then there will be a longer panel discussion involving both Dr. Kardia and our next speaker as well. So everyone will get their shot, but I want to get us back on schedule.

Kevin?

DR. FITZGERALD: Thank you very much, Professor Kardia, for those forthright comments. I just have a quick question. How much, roughly, of your comments do you see is specific to the United States, and how much of this would flow over into some of the other large population studies that are being done around the world in different countries?

DR. KARDIA: Well, that's a difficult question to answer because in other countries they have very different systems. I mean, in the U.K., where they have a very different regulatory system around genetic information, they're not going to have the same kind of issues. We could go piece by piece. It's very specific to each one, depending upon how regulatory decisions are made and what their current standards are.

DR. WILLARD: Joseph?

DR. TELFAIR: Dr. Kardia, thank you again. My question has more to do with the practical applications. You alluded to that throughout your discussion. I'm wondering

if you can give some specifics to this. I mean, you concluded that it's premature to mount such a study like this, but throughout your discussion you were alluding to specific ways that the process may begin and how things were done. You sort of painted a broad picture of it, but I'm wondering, given your experience, particularly at Michigan, particularly with the group that you work with, the community-based involvement part of it where there are several principles for how you work with communities and how you work with those groups, and also ways of doing professional education, I'm wondering if in your experience and in your efforts, have there been specific activities you've undertaken or specific efforts you've made that have been successful in getting things done? If you could speak to that, I'd appreciate it.

DR. KARDIA: Sure, sure. I'd be glad to, because this is something I work hard on, and I have been amazed at how disparate the solutions are.

At the community level, my understanding of where to start is really in the relationship of genetics to self, to family, and to humanity. What are people interested in? How am I related to my brother and sister? Very basic concepts, things that make them feel good about understanding that I have genome in every single cell. It's very basic, because when you move to here's a mutation, it causes disease, you have a 25 percent risk, all of a sudden they have no context, no personal context with which to use the information. Now, if the doctor says take this pill, they can do that, but they don't retain their genetic information, right?

Now, health professionals are on the opposite end of the spectrum. They want basically the news they can use. I've given many different grand rounds to doctors on cardiovascular disease. The long QT syndrome, sudden cardiac death is a great way to get people excited about genetics, but then they say how am I going to use that? So there's this gap. Now I've got information, but how does it meld with my current practices? You can see that the needs are very different, and I think that one of the things that this also makes me aware of is that you can see by that big difference why the public would be suspicious. The public doesn't have the basics. The medical practitioners want to use the information, and there's not a connection in the middle, even, where doctors and patients can really talk about genetics in a common language that would help them build that trust so that genetics information doesn't become a liability but an added value.

DR. WILLARD: Okay, we have Francis first.

DR. COLLINS: Thanks, Sharon, for a very thoughtful presentation. You've covered a lot of territory in terms of topics that are at the interface of genetics and society and public policy that this committee has been wrestling with since their founding. Obviously, you have a great deal of experience in the field of epidemiology, so I think your opinion carries a lot of weight.

Let me challenge you, though, on the notion that if we just sort of put this off for five years, that might be a better solution than starting it now, because I think a number of the areas that you have pointed to as being potential barriers are unlikely to improve without some stimulus, and a project of this sort in many ways could provide a useful stimulus.

Having been in Washington now for a dozen years, I can tell you that agencies and regulatory systems, and even public policy decisions that relate to legislation, like genetic nondiscrimination, rarely act unless they perceive a need, and even then it takes a while. A public project with this kind of visibility would, I suspect, be a very valuable additional impetus for taking action to plug some of the many regulatory and legislative issues that you've touched on, and without this kind of project I suspect they will go slower.

Similarly, you point out the issues of public misunderstanding, of scientific communities not necessarily understanding each other and working together. Would not a project of this sort which, if mounted, would be a very visible national enterprise, I suspect more visible than the Genome Project because it would involve lots and lots of people, just regular people, would that not be a wonderful opportunity to try to achieve some of those educational steps for the public, for the media, for public policymakers, and for the scientific community? Because some of the things you said about the inability to work together were said about the Genome Project in 1988 as a reason why it was never going to work, and it probably would not have brought those communities together had there not been a project to provide the glue.

Furthermore, in terms of how this would stimulate the field, you mentioned the concern that maybe this will basically fund a small group of people who will get very rich on the funding from this, and everybody else will suffer. Again, the model would be to have all the data publicly accessible. So having a data set of this sort I would think would be, just as the genome sequence has been, a real stimulus to a field. You mentioned yourself how nice it would be to have the data.

So let me just challenge you in terms of the timing issue, because, of course, this is a long lead time enterprise. You're not going to get anything out of this project until you've set it up, until you've enrolled a lot of people, until you've started to see a lot of incident cases. If we don't start now, we won't really have much useful information five years from now. If we don't start until five years from now, it will be ten years before we have these kinds of data.

Are those arguments so compelling in your mind that it's better to wait, as opposed to trying to use this, which I'm obviously proposing, as a way of trying to address some of the things that you're most concerned about? I'd like to hear your thoughts on it.

DR. KARDIA: Sure. I guess at baseline my, I'll call it, opinion that we need more time comes from my human experiences, that researchers not being able to work together because of the disciplinary disconnect, and that's a real issue, as well as turf wars. Right now I can tell you from an epidemiologist's point of view that I get funded for collecting data, not analyzing it. The NIH will cut off the fourth year where all the analysis is to be done as long as the recruitment is done. There is not a lot of appeal for genetic epidemiologists who analyze data because we can't get it funded by our peers. Collecting data is what does it.

I think the other thing is that there have been some inroads in terms of these regulatory agencies. I mean, the FDA is really having to struggle with this, even if it's just in the generic case of the BiDil drug. But where in the plan is the resources for the infrastructure? Why aren't we doing a national genetics education? I don't believe education in the mix of research is the way to do it, because it's at different ends of the spectrum. I mean, what you're trying to accomplish is about the genetics of disease and disorders. Where people need to start is way far away from that in terms of their own personal relationship with genetic information.

So it just seems to me that there needs to be some other things in place, and believe me, I understand. Ten years of working on the Family Blood Pressure Program, we're now just getting to the point where we're getting some exciting results and the ability to do things. But there was the natural pressure within the system to show, just like a corporation, quarterly progress that I think actually dismantled much of what would have been, basically, the advances that we needed to make in our complex understanding of genetics rather than going

for the single-gene paradigm. There's a huge amount of force right now to do the single-gene paradigm.

PARTICIPANT: That's crazy.

DR. KARDIA: It is crazy. We're suffering. Science has got fashion in it. The HapMap is fashionable. If you don't put a grant in with the HapMap tag SNPs, you're not going to get a good score. From a human perspective, I think we have a lot to get over with this large population study.

DR. WILLARD: Thank you for that. I'm going to let you catch your breath and I'm going to ask others to hold their questions until we come back to the panel discussion, where everyone will get another crack at you.

(Laughter.)

DR. WILLARD: Our next speaker is Richard Marchase. He is vice president for research and the senior associate dean for research at the School of Medicine at the University of Alabama at Birmingham, but today he is here representing FASEB, the Federation of American Societies for Experimental Biology. His presentation will be followed by a specific Q&A to him, and then we'll invite Sharon back for a broader discussion involving everyone.

Dr. Marchase?

DR. MARCHASE: Thank you very much. The Federation of American Societies for Experimental Biology is a coalition of 23 member societies representing over 70,000 scientists in diverse areas of life science and medical research. Prior to a decision about undertaking a large population study in the U.S., we at FASEB agree that the broader scientific community should be given an opportunity to comment, and I thank you for allowing us this opportunity today. Such consultation will surely be important for the technical and design considerations that will be inherent in this study, but these are not the issues that I will be addressing or focusing on primarily today.

In developing a response to the questions posed by the organizers of this session, discussions were held with FASEB's Clinical Research Subcommittee, or NIH Issues Subcommittee, and member societies, including the American Society of Human Genetics.

I'd like to begin by saying that FASEB recognizes the potential of such a study to improve people's health. The policy issues raised by the committee's task force, described in the background information that Dr. Willard already has described, are all important issues to address. When we at FASEB looked at what the policy issues were that were most critical to us as the broad representative of the scientific community, we focused on three: the prioritization of this study relative to other large-scale studies; the study goals, how well the study is designed so that useful data can be produced; and the cost and possible effects on research project grants, investigator-initiated studies, and other initiatives at NIH.

Relative to the first point, the prioritization of this study relative to large-scale studies, we are interested in the dialogue that will allow us to put this study into perspective relative to the other large-scale initiatives that are currently being undertaken. This includes things such as the Children's Health Study and recent initiatives toward increasing NIH's presence in clinical and translational initiatives. Dr. Zerhouni's roadmap initiatives are already on the table as important ways for the NIH to expand the relevance of its mission, and we are interested in seeing how this study will shape up, how it will be prioritized relative to the studies that are already on the books at NIH.

The other point I would like to make here is are we sure before we initiate this study that the other long-term studies that have been referred to before have been mined as much as they could be to allow the appropriate data that would set the stage for such a study as the one being described here?

The second point has to do with study goals and outcomes. A major challenge to the usefulness would be how well will the outcomes of such a study be used by the scientific committee. Clearly, there's been a lot of thought to the way the study would be designed, and we are not going to in any way doubt that this study would go forward in as efficient a way as possible. But there are some questions -- for instance, those raised by Dr. Kardia -- that we think do need to be considered in much more detail than they have at this point.

How will the data be collected, stored and made available? The lack of appropriate electronic medical records has already been referred to. There are questions about how environmental data would actually be collected, and there was a lot of discussion in the background information about the necessity to develop new techniques to, in fact, make sure that environmental data were going to be appropriately handled by these studies. How will the genetic and other personal information be protected? Again, an issue that Dr. Kardia has addressed very well. And does our current health care system have sufficient technology and infrastructure to support the data collection and the data sharing that would be necessary to make this study a success?

Lastly, there is this idea that a need might be found to restrict or focus the study more. We've talked about pilot studies and what advantages pilot studies might have, and this is going to plan for the last point that we're really going to focus on, and that is the skepticism that Dr. Fink referred to that was characteristic of the scientific community at the beginning of the Genome Project and which we are concerned would also be the first stage of recognition of this project by the broader scientific community, not just those who are geneticists and not just those who might have biases against geneticists, the social and behavioral scientists, but rather the broader range of wet lab and scientists that FASEB to a large extent represents.

The primary problem that we foresee here is that this is a very expensive endeavor, and it is being proposed at a time when NIH funding is not increasing and when success rates and paylines for all grants, including R01s, are at a very low ebb. If I could advance to the next slide, I'd just like to show you some data that I think most of you are familiar with, but this has to do with the percent change in the NIH budget. Those numbers appear a little small, but what you can see is that in the mid-90s there were percent changes that were on the order of 5 to 7 percent. During a doubling period, the changes went up to 14.4, 15.9 percent. For 2004, there was a 3.2 percent increase in the NIH budget. The 2005 budget is not set but it is likely to be 0 to 1 percent in terms of where it will be relative to the 2004 budget.

Now, these low increases in the NIH budget put a very significant burden on investigators who are submitting their own ideas for funding at the NIH. Much of the buildup that occurred in the Genome Project and much of the overcoming of the skepticism that Dr. Fink referred to took place during times when success rates at NIH were not being challenged by the lack of discretionary income that was available.

The next slide, in fact, shows those success rates from 1995 until 2004, and

you can see that during the very largest buildup and the completion of the genome study, success rates ranged from 27 to 32 percent. During the period of the doubling, these success rates were very high. This allowed a third of the grants that were submitted to be funded. That's still not a very large number, but a lot of meritorious research was, in fact, included in that one-third. If we look at the success rate for 2004, you can see that there's a significant drop, about a five-point drop, as we are suffering through what's called the hard landing at NIH that's following the doubling. We expect that success rates in 2005 will drop even further.

Now, as I said earlier, FASEB believes that the funding for investigator-initiated research projects should remain a high priority at NIH. Therefore, an important question to our community is what would happen to success rates if R01 funds were cut in order to fund this study? We've gone through a hypothetical example that's shown in this next slide.

No one knows exactly what this study would cost. The estimated cost could be as much as $3 billion, perhaps even more. If we were to take roughly a tenth of that, $350 million taken out of the R01 budget, that would be approximately 1,000 fewer grants that would be awarded. Based on 2004 data, the success rate for R01s would drop from 24.9 to 21.3 percent. We are very concerned that the allocation of this size of a pot to this project at this time during flat funding periods would be highly detrimental both to this generation of biological scientists, as well as to the next generation. It's already very difficult for a young investigator to think that as he submits a grant, he has a 24 percent chance of success. When that success rate goes down to, say, 20 or even below, it can be a very discouraging thing. In the late '80s and early '90s, we saw how discouraging such success rates were to the influx of new investigators and to academic research careers. We would just not want to see this study be funded in a manner that would both hurt the entry of scientists into our research pool, as well as the human cost to our scientists who are already working. If 1,000 fewer investigators are funded per year because of this allocation, what does that do to the faculty in our biology departments and our medical schools that currently are already there and struggling in many cases to assure that their research careers are going to continue to flourish?

This isn't a welfare program in any way. These are scientists who have been selected through a very highly selective process, and they're talented. They are contributing to the kinds of advances that are going to allow the next generation of medical discovery to lead to real cures.

FASEB's longstanding principle has been that investigator-initiated, competitive, peer-reviewed grants should remain the core mechanism for distributing research funding. This mechanism does allow highly skilled scientists to propose a direction and priorities for future research based on their own expertise and preliminary data. Funding of these proposals occurs only after very rigorous peer review. These grants have been the foundation for much of the progress to date in biomedical science, and by placing most of the resources in investigator-initiated peer-reviewed research, NIH ensures that federal taxpayer dollars will support the best science.

Therefore, this study should be undertaken only if funded through sources that do not compromise investigator-initiated projects.

In conclusion, we recognize the numerous potential benefits of such a study for public health. We are not in any way disputing that. This is also a visionary type of study that, in fact, could help to break the flat-level funding that we are experiencing. It could

perhaps be the kind of vision that Congress would get behind and new monies might be allocated. We are concerned, however, that in a time when discretionary spending is very limited, with the Iraq war and the response to our hurricanes, that there may not be new funds available in addition to the existing monies that are already at NIH.

I commend the committee for grappling with these issues now and thank you for the opportunity to bring these concerns of our bench scientists to you today.

DR. WILLARD: Thank you, Dr. Marchase.

First I'd call to see if there are questions specifically for Dr. Marchase before we open it up more broadly.

Emily?

DR. WINN-DEEN: So I guess I'm a little confused. Who do you think is going to get the $350 million a year if it's not people in the science community?

DR. MARCHASE: Oh, there's no doubt that it will be people in the science community, but there's no doubt that this kind of a shift will cause a distinct difference in the funding that will be seen, for instance, in the physiology community or in the pharmacology community. We have many constituent societies in FASEB, and a shift of this magnitude could very definitely disenfranchise some investigators and empower what we hope would not be a small group of investigators within the genomics community, but there are concerns about the breadth of funding that would be taken away from other disciplines.

DR. WINN-DEEN: Okay. So it's not the overall magnitude. It's the shift from wherever it is today to a different group of people who would be receiving that money.

DR. MARCHASE: Exactly. There are cellular molecular studies that are very important to the way we understand diseases today. These are being carried forward by scientists who are not necessarily geneticists. We're just a bit concerned about a drop of the magnitude that might be seen if this were done out of an existing flat budget.

DR. WILLARD: Muin first, and then Francis.

DR. KHOURY: Thank you for your comments.

I kept hearing the word "study," and you mentioned that this is a study. I would like to react to this and get your thoughts on this idea, too. I've been interacting with a lot of the international biobanks and cohort studies, like the one in the U.K. and the Canadian and other places, and the way they sell their studies is that they don't call it a study. They call it a resource, because collecting information on a large number of people to be followed over time is not an individual study. It's a resource that could lead to thousands, if not millions, of studies that could be generated in the future.

So in that context, or prism at least, would you still have the same -- I realize all the comments you said are probably true in terms of shifting the funding in the short term. But in the long run, if you think about a national effort such as this that could be a resource for studies, how would that --

DR. MARCHASE: Yes, absolutely right. There's no doubt in my mind that in the long term, this is a very important resource that would be appropriately used by physiologists, anatomists, the whole spectrum of biomedical scientists. We would applaud, in fact, the fact that this resource should be made available. We're just very concerned that, as you say, in the short term it's not done in such a way that it jeopardizes the scientists who are currently working and who are going to be entering the fields that are not necessarily going to be given the opportunity to do the short-term work.

We would hope that, as I said, this could be the visionary kind of link that would allow us to, in fact, increase funding for the biomedical sciences.

DR. WILLARD: Francis, and then Debra.

DR. COLLINS: So, Richard, I appreciate your thoughtful comments, and certainly all of us at NIH are deeply concerned about the trends in terms of support for R01 investigators. The curve that you showed is likely to get worse in the current circumstances.

Yet when I talk to leaders who are in a position of being able to try to turn that around, oftentimes what they ask for is what is there out there in the way of a signature initiative that would enable some increased enthusiasm for biomedical research at a time where, frankly, there is not as much as there was a few years ago. There's a sense we gave you your doubling. Okay, that should be good enough. As we all know, the benefits of the doubling have been substantial, but they're being eroded rather quickly as that very different kind of mindset has set in.

So I agree with you that it would be pretty nigh impossible to initiate a program of this magnitude in the current budget climate. The idea of actually losing 1,000 new grants on the basis of this kind of a project is just not tenable. But I do think, picking up on your remarks a minute or so ago, that there is a real opportunity here for the biomedical research community to identify one or two flagship initiatives that are compelling in terms of their benefit for public health. Whether this is one of them or not is something to be discussed and decided.

But I think the worst thing we could do right now would be to hunker down and say, well, you know, maybe we can just somehow get by with the current circumstances, and not take the opportunity here to try to identify some new things, which is the only way I think we're ever going to really generate that kind of enthusiasm and energy for getting back on a more progressive course.

So your points are very well taken. Again, I don't think anyone is proposing that a project of this sort could be initiated from existing funds. It would not be tenable.

DR. MARCHASE: Yes, I agree completely, and I do think that this is the kind of visionary project that might move us off the stagnant place where we are right now.

DR. WILLARD: Debra?

DR. LEONARD: An underlying theme that I'm hearing both from Dr. Kardia and Dr. Marchase that I don't think is being articulated is a strong holding to the current academic system as it exists. I think there's an impetus for change to that academic system from the NIH Roadmap valuing large group efforts, collaborative types of efforts, and there are certainly underlying gender issues and minority issues that are not -- at least the gender issues are not supported by the current academic tenure system and the tenure clock.

I'm wondering if some of the dis-ease with what we're talking about here and moving towards this initiative isn't shaking the underpinnings of the academic system of having to have two R01s and a project on a P01 or a score in order to get tenure within the designated six to nine years. Does that system need to be reevaluated by the academic community in light of the funding and the research initiatives that are currently being valued by the NIH and other organizations?

DR. MARCHASE: Absolutely, and I think that our institution is one example, but you'd find institutions across the country that are trying to grapple with these issues, especially in these departments and programs that are very highly leveraged because of

their involvement with extramural funding sources such as NIH.

We appreciate many of the things that NIH is doing; for instance, the idea of recognizing multiple principal investigators is certainly a step in the right direction to allow us to rethink what it is we should do to ensure that our academic enterprise is able to go forward in a productive manner, and with an appreciation for the fact that things are different now and big science is going to be a very important part of how we go forward.

On the other hand, even if big science becomes an increasingly large part of the NIH budget, I believe that it is not just a parochial interest for us to maintain an emphasis on the kind of research grants that have given us so much in the way of advancements and disease-curing power. We have very bright people out there, both men, women, young and old, and we want to assure that the individuality of the way they think doesn't come asunder because we go too far to the big science point of view.

DR. WILLARD: Steve Kaminsky?

DR. KAMINSKY: I had one question. Since you had the clinical group associated in one room, did they articulate whether they thought that if this were to go forward it would be better as a trans-NIH effort, or would it be best to actually place the project in one institute or one center from the standpoint of really maintaining a real focus on getting the resource out there and managing the resource, much like the Human Genome Project was back in the early '90s?

DR. MARCHASE: We didn't address that at all. I mean, I think that certainly this is an initiative that is going to benefit all of the NIH institutes if it goes forward. Obviously, everyone would favor a system where the management was as efficient as possible.

DR. WILLARD: Sam, you're next up.

DR. SHEKAR: Thank you very much.

Dr. Kardia, you had a number of very relevant points, important points raised about the infrastructure issues and societal issues associated with developing a large study, but there's also a great phrase: "Don't let the perfect be the enemy of the good."

One of the concerns that I have been listening to in your comments is an assumption, perhaps, that we can achieve some perfect societal and infrastructure development in order to then begin this study. We understand that there needs to be significant progress made in these areas. For example, NIH and HRSA currently are engaged in a five-year, $2.4 million contract to educate health care professionals through NCHPEG about genetics and the use of genomics in their practices. But it's understood from the very beginning that this is an iterative activity, that this is not the ultimate be-all and end-all for education such that all health professionals in this country will know everything they're supposed to know in genetics/genomics.

So I guess my question is what are the activities that could occur in the next five years, say, that would need to take place in order to achieve this level of support that you're discussing, and what can realistically be achieved in the current systems that we have and with the current social activities that we engage in?

DR. KARDIA: That's the key point.

DR. SHEKAR: In the absence of the study.

DR. KARDIA: Right, and I don't think I'm being a proponent of perfection. But just in the example that you gave, the $3 billion price tag to the $2.5 million is the huge discrepancy. If you put $100 million towards genetics education of the nation, including health

professionals, then you might actually get somewhere. But $2.5 million is not a lot of money. It's just not, to do the kind of infrastructure building that you really need.

The same with policy research. How much dollars are going to genetics policy research and how we do this? Shouldn't it be on the same scale? I mean, it's the out of balance, and I know epidemiological studies are expensive, and that's not the issue. The part about the academics, I would love to see academia change. I think the interdisciplinary way to do things is it. And yet, how do you get the funding to do that? It's not out there. I've been lucky enough that, for a lot of reasons, people will come to me for genetics. So I'm part of a mind/body grant. I never thought I would do anything with mind and body. And I'm a gene/environment interaction core for this whole set of social and behavioral scientists.

But the gulf is so big. I mean, I have to teach them what a polymorphism is 20 times before we get anywhere. Again, it's a balance. If you're going to spend $3 billion on something, spend $500 million on the infrastructure, because that really then gives you something you can work on. But it looks out of balance right now. You're going to go do this great science, but the rest of it's not there.

DR. WILLARD: Okay, they're queuing up now. I have Muin and then Julio, then Debra.

DR. KHOURY: Sharon, can I pick up on the comments that were mentioned earlier and sort of try to reiterate it in a slightly different way? What I'm hearing you and others say is that big science like this in the absence of a context where big bucks are going to create a resource that could be used in the future, when you say we're not ready for it, it's because of the contextual, all the things around it, like education, informed consent, the ELSI, the policy, the translation, the lack of health systems awareness, and the lack of infrastructure. I think the committee is probably taking note of that and will be further discussing it.

One specific point I have in mind and I wanted to ask you what you meant by it. It's one of the sayings we have at CDC: "Think genomically and act locally." That's why I guess we've kind of acted locally through the state infrastructure to sort of build up the capacity to do the good work that will come out from the Human Genome Project.

You did mention that as we embark on studies like this, environments are local, there's a lot of changes and exposures, the genomes are local. How would you think about a two-prong attack here? One is to build the big science, at the same time building that infrastructure, and perhaps the science can go with that infrastructure given the idiosyncrasies of genes and exposures per locale? Because if you develop, let's say, a Michigan genome initiative or a Washington State genome initiative --

DR. KARDIA: I'm working on that, Muin.

DR. KHOURY: -- where you do the kind of big science in the context of public policy, where you educate, you do informed consent, you collect data, how would that work given all the stuff we've been talking about here?

DR. KARDIA: Well, there's a lot of ways that it could work because, for instance, the last three years working with the Department of Health, creating relationships so that what we have is a broad access point or bridge between academia or the departments of health, then allow us to really garner the resources of populations that a department of health has, and then use the good science and the measurement in academia.

One of the key things in the -- I'll call it study design, is being able to have enough people that are representative of basically the population you want to serve so that you

can do the replication studies within that population. I have been struck over and over again just how much we group unlike people. We say African Americans in this country. There is a decline of allele frequencies from the north to the south in different alleles, and we tend to just pool everybody together. If they're white, they're in this group; if they're African American, they're in this group. There are differences in allele frequencies, genetic factors, across populations, and very big differences in environmental factors.

So my sense is if they're really going to do this well, you have to match the population you want to serve with the genetics research. So I would say focus in on big cities where the biggest public health burdens are going to be, and try to do it well so that local and state departments of health, as well as local clinicians, can actually use the information that are coming from their study. That would be one way to do that, and then it affects the local policies at that state level to be more specific in terms of the cases. In Michigan, we have a huge dioxin problem. Dioxin/gene interactions would probably be top on the list.

With the great technologies these days, the genomics, the proteomics, the metabolomics, we can measure incredible things at all of these different levels. That would be another suggestion. Right now, a pure genetic approach leaves a huge gap between finding an association and moving it into the treatment and prevention without the biological causation to back it up.

DR. WILLARD: I think, just to jump in before we go with questions, in considering "genetics and genomics," we're rather inclusive about the particular technology and the level of omics that one might bring to bear on the particular questions.

DR. KARDIA: Good.

DR. WILLARD: Julio first, then Debra.

DR. LICINIO: I have a comment and a question to you, Sharon, and hopefully Francis Collins could also comment, which is that these large genetic-based initiatives have been mostly bench-based so far, like the Human Genome Project. They didn't have to deal with living individuals. In this project, the playing field changes completely because you're essentially proposing to follow people up for a long period of time and look at health outcomes in the context of their genetic material.

So one analogy that could be made, and it was said in the first presentation, is that the minority should be included, maybe even overrepresented, so that you can be sure that they are there in equal numbers.

So think about this. I work with one of those populations, and the rate of health insurance is very low. So if you're going to include people who only have health insurance, the study is very biased. If you include the population at large, which will include a substantial proportion of people who don't have health insurance, you just sit there, you're insured yourself, you're funded, and you watch these people over time get sick, and in inner cities with people who have high rates of asthma, depression, hypertension that's poorly managed, very poorly managed, diabetes that's also very poorly managed, obesity that's also not treated, and you just watch these people get sick over time and document how sick they get and do nothing about it, and then collect the DNA and try to find the cause of their sickness, I think it's very unethical.

On the other hand, it's not feasible to give health insurance to all people who are uninsured. So if you think about this, you'll find a very poor population in the Third World, let's say in India or Africa or somewhere, and they're starving, and you go there and you want to

follow them over time, and you sit in your cabin and you have your food and everything, and you live a comfortable life, and document how these people are suffering over time. It is what's happening in this country.

You could say if we don't go there, we're going to have the same outcomes anyway, so we're not doing anything bad to them. But once you get involved, there is a degree of social responsibility that I wonder how you can justify spending $3.5 billion on the entire project to watch people who have no access to health care get sick over time.

DR. KARDIA: So why not a model where the research is also health care? Why not have it incorporated? If a doctor is going to give a clinical exam and make a determination, why not do the health care on the spot? It's one of the reasons why -- I really understand this, and it's one of the reasons why I'm trying to move to the community-based participatory learning, how to do this, because the distance between the researcher and the participant leaves the participant basically isolated. There's no real engagement.

At the University of Michigan, we've got these incredible community-based participatory researchers, and they are doing things I would never think of. Their asthma project has money in their budget to help the asthmatics with whatever they need. If they need a new couch, if they need a vacuum cleaner, if they need something to actually help, it's in that budget. I don't know why something like this couldn't be unique in the way in which they offer feedback. If a doctor is already seeing them, what's the difference between writing a prescription, finding generics, and working with communities? You would be surprised how much communities care about the people in them, even if they're disadvantaged. You can work with that.

I mean, things that have worked, for instance, around violence programs. How do you get inner city poor people to work together is by working with people to support each other. Genetics researchers have never done this before. Why aren't we using some of the things from the social sciences that have worked in terms of community support?

DR. WILLARD: Debra?

DR. LEONARD: Well, Sharon, in your discussion, you rang a bell. The Human Genome Project, Francis, had 10 percent of its budget dedicated to ELSI issues. Five percent? Five percent. Sorry, I got the percentage wrong. But it's a lot of money.

DR. KARDIA: Better than nothing.

DR. COLLINS: $20 million a year.

DR. LEONARD: So can we redefine ELSI to have another E on the end, ELSIE, for education? Since education would be such an extremely important part of this project. I mean, ethical, legal and social also are big, but there's such an educational component to this that I don't even know if you've considered a portion of this budget going to these issues or not. But if you have, I would encourage education to be a significant portion of that.

DR. COLLINS: Can I answer?

DR. WILLARD: We'll let Francis answer that.

DR. COLLINS: Absolutely. Again, I hope people have had a chance to look through the tails of the report that's under Tab 4. This group of more than 60 experts that worked over a period of more than a year dealing with many of the issues we're talking about this morning certainly came to appreciate just how complex this is, and while all the nuances of those conversations are not captured in this 25-page document, I think there is a lot of information there that would be very relevant to some of these conversations, and certainly a

need for education as a component of this was absolutely clear and, as I'll talk about later on today, especially the need for public consultation about the wisdom of undertaking such a project before you even started was highlighted by that group.

I have to tell you, that group came into this discussion pretty skeptical about whether this was a study that had sort of found the right time in history to be undertaken, much in the way that Sharon has described, and many of them, people like Eric Boerwinkle and Greg Burke, are fully aware of the complexities of trying to marry together these disciplines.

One of the things that I don't think comes through as clearly in the document as it might, and it hasn't in this morning's discussion, is just how critical it would be to utilize this kind of a study as a means of improving our ability to do environmental assessment. This is not a study of genomics. This is a study of genes and environment, and particularly how they interact with each other. If you don't have the environmental data, there's nothing to study in terms of those interactions.

I'm sorry David Schwartz is not here today because, as the new director of NIEHS, he's gotten very involved in many of these discussions and has a lot of really interesting ideas about ways that we might improve the technology for doing that kind of environmental assessment, not just sampling the environment but sampling body burden and, most interestingly, sampling biological response to whatever it is that that body has been exposed to, using genomics and proteomics and metabolomics. There's a lot that could be done there.

So as we talk about this project, yes, please, think about all these dimensions, the environment, the technology development which would need to be part of this. We don't have the right technologies to do any of this right now, to do it really well. Does anybody in the room think we have appropriate tools to measure dietary intake right now? I mean, they're ridiculously antiquated, and we desperately need to do all kinds of new technological approaches there, and there are possibilities to do that.

So think about that, and think about the education, the ELSI component. If this were ever to get off the ground, it would have to have that kind of very complex set of components in order to justify itself, and in order to do the kind of public good that we want.

Finally, I've just got to say, if we say this is a project that shouldn't happen now, let it not be said that the reason was that somehow the scientific disciplines couldn't get together to work on it. That would be truly tragic. If this is a project that's going to benefit the public, and if we could figure out how to pay for it, then let's do it and let's not put up barriers about our own sort of communities being stuck in current models of how we can't get along. That would be really sad.

DR. WILLARD: So we'll let the record show that that answer was yes to your question.

(Laughter.)

DR. WILLARD: Jim?

DR. EVANS: Thanks. I just wanted to really reiterate something that Gerald Fink said this morning that I think is very important, that at a fundamental level the scientific issues become policy issues, and that is that we obviously don't want to invest huge amounts of resources in something where we haven't looked critically enough at the potential outcomes. So we're talking, for example, about the physician taking care of the patient, the patient with asthma, et cetera.

As a practicing physician, I have a certain inherent skepticism about studies

that require, say, 100,000 people to show a significant P value, because my question as a physician is, okay, that's statistically true, but is it relevant for my patient? While I think there are some very tantalizing examples -- for example, age-related macular degeneration -- I think that the unfortunate general consensus is that a lot of the diseases we deal with, like diabetes and hypertension, and indeed I think the studies show, are going to be extraordinarily complex, with many genes and many environmental factors contributing.

So if we embark upon and are successful with a study that has a half million people, a million people, and we are successful in identifying polymorphisms that contribute 2 percent or 3 percent of the genetic component to a disease, have we ultimately gotten good return on investment for that? I think that, again, there are some very tantalizing studies that I'm very excited about that indicate that maybe if we take into account environment and genetics, we will be surprised that an inordinate amount of risk is dictated by a few genes. That would be exciting.

But I guess my plea would be that we have to look very critically at the experience of case/control studies and in other countries, the large cohorts that are going on, to see if the kind of return on this type of thing will be a tangible return and a useful return for patients. Ultimately, we're not going to be satisfied with extremely incremental, small analyses.

DR. WILLARD: Joseph?

DR. TELFAIR: Thank you. I appreciate James' comments because they were relevant.

I want to go back to something that I brought up a little bit earlier, because I still am not satisfied with the answer. It has to do with just the practicality of this question, independent of when you start, that sort of deal. I also wanted to address this both to Dr. Marchase as well as to you, Dr. Kardia.

It seems to me that one of the things that we have to struggle with in terms of making this recommendation, or even looking at a recommendation, has to do with addressing the way that we sort of interact with one another both as scientists and as scientists with the public. Clearly, in the presentation from Dr. Marchase, there were a lot of issues related to within that group of concerns about what's going to happen if this occurs.

It seemed to me, though, is that a question, as Dr. Collins alluded to, something that's really going to limit us, or not? So I'm going back to the question of how do we make it work? If people are concerned about those things, how do you sort of bridge the gap, then? Because reality is, independent of where the funding is going to be, at some point you've got to make a decision, either you do or you don't. Yes, we're going to try to make this happen, or no, we're going to continue to do what we're doing. It seems to me that in order for us to be able to make a good decision, we need to have some real concrete yes or no, you should go forward with this, yes or no, you should not. It's a little frustrating to me to kind of dance around it. I'd just like to get an opinion on that.

So I'll start with you, Dr. Marchase, and Dr. Kardia, if you want to comment, that's fine. Thank you.

DR. MARCHASE: I think the bottom line of whether you go forward is going to be a very difficult situation. I would say that the take-home message that I would try to bring to you is one in which we have to do this in a manner that does not completely disrupt the ongoing scientific community that has been so productive in the past and that does not discourage new investigators from coming into the system. If, as Francis suggests, we can do

this as one of the projects that really moves us off the flat-line funding that seems to be the way that biomedical research enterprise is viewed now by the government, I think we'd be better off doing it.

We need to assure, for our country's good, for our patients' good, that in fact we are going to have scientific progress going forward. We cannot do this study if it means that we're going to be absolutely debilitating 90 percent of the scientific disciplines that make up the biomedical enterprise. If we can do it in a way where it's clear that the skepticism by scientists who are not necessarily the geneticists is going to be overcome, if it's going to be done in a way where other disciplines are going to be able to be funded at reasonable levels, then I think there are real advantages to having this resource be created. But the need for further investment in the biomedical research enterprise cannot be minimized.

DR. KARDIA: I think I would agree with many of those statements. You could start right now if there was basically the plan that really does address the issues of how do you take care of the person, the participant, all the way up through the investigators, as well as the system in which the results spill out. I mean, 5 percent on the ELSI was a great start. But for something like this with these implications, I'd say 25 percent of your money has got to go for your infrastructure of what are the results you're actually going to end up with, which is in the public, in the regulatory systems.

In terms of interdisciplinary work, maybe it could be a model for doing that, but the rubber would hit the road as to whether or not it was real or lip service, whether or not it was going to gut the funding of other members of the scientific community or not. I can't tell you how many times the social epidemiologists go right at me an say it's a big waste of time, a total waste of time and money; why are you doing it? You know, when I look at the actual statistics, the polymorphism that explains this amount of variation and poverty, racism, the other social policies, I'm a logical person and I have to say you're right.

But if we integrate them, really integrate them -- and this is where my skepticism comes -- that integration, how long does it take to learn a field? To really get good enough that you can be a quality investigator takes years. I'm not sure that just bringing people together on a particular project does it. There's got to be other mechanisms in there, as well. The roadmap is great. How many people are they funding?

DR. WILLARD: Muin?

DR. KHOURY: They're all excellent points. I know we've kind of been dancing around the point of a dichotomous yes/no answer, and I detect some of the frustration here of when do we move forward, when do we not, with respect to a complex question such as this.

Let me put things in the context of history a little bit and then ask both of you to comment on this. We've already spent millions, if not billions, of dollars to get to the point where we are right now with mapping and sequencing the human genome, okay? I mean, the benefits so far have not been great, but we're on the way. I guess the question is how do we move forward with a bolus of investment that would allow us to translate the human genome sequence and the related technologies to population health? That's what we're talking about here, sort of how do we bring the genome to the health of the population.

Now, the initial project went on with the funding of the 5 percent of ELSI to appease some of the anxieties and the issues that were deemed to be too complicated and the ethical issues here. I heard already the issue of the "E" being added to the ELSI, but I'm hearing

Sharon and others saying that in order for this massive public health research project to move forward, that perhaps one thing to be invested in is something more than just the education and individual-based ELSI but more of a population-level ELSI. That's what we're talking about, which is public policy, public education, infrastructure for health departments, et cetera. Now, how do you envision that 25 percent would be invested, assuming there are new monies coming in? I mean, how would that work?

DR. KARDIA: I plead the 5th.

(Laughter.)

DR. KARDIA: I mean, that's very complicated. You would have to have some kind of -- I would call it a strategic plan of where the greatest need is and where the greatest lack is, and there has to be that prioritization. I mean, not having regulatory bodies understand genetics seems to me a major liability. Not having health professionals understand genetics and not having the public understand genetics seems like a major liability. Not having departments of health have really anything more than newborn screening as their genetics seems like a major liability.

The interdisciplinary stuff we probably could work through, but the others I think would take a significant embracing of the issues.

DR. WILLARD: Kevin, and then Sylvia.

DR. FITZGERALD: First of all, I'd just like to ask Dr. Kardia, my understanding is we don't have your written comments. Would you be willing to give us a copy of what you --

DR. KARDIA: Absolutely.

DR. FITZGERALD: Great. Thank you very much.

Secondly, then, I'd just like to pick up on something I've been hearing now more and more, and since we live in the world of acronyms here in Washington, I'd like to ask a couple of people around the table would it be a deal-breaker to pursue a PHELSIE, P-H-E-L-S-I-E?

(Laughter.)

DR. FITZGERALD: In other words, if we were to go ahead with this kind of project, integral to the project would also be the goal that we claim for the project, and that is public health. So in other words, unless the structures were built in to say if this individual is coming in for research, then that individual's health care is also taken into consideration, as part of the project, is that a deal breaker? I'm just wondering.

DR. WILLARD: Muin?

DR. KHOURY: Actually, the term "PHELSIE" has been used before.

(Laughter.)

DR. KHOURY: Toby Citrin, from the University of Michigan, has written a chapter in the Genetics and Public Health book in which he sort of elaborated on -- and actually in some other reports as well -- on the differences between the individual ELSI and the population ELSI. I think all the issues around education and policies and infrastructure and health care systems are the kinds of issues that the original Human Genome Project did not take on because they didn't have to at that point. They were just mapping and sequencing the genome. So the word "PHELSIE" already exists.

DR. WILLARD: We're going to go to Sylvia first, and then Julio, and then Joseph.

MS. AU: I have to echo what Dr. Kardia said, that 5 percent of a research budget to deal with such a broad, major important component such as PHELSIE, which you should add an "F" to, too, because there are the financial issues --

(Laughter.)

MS. AU: So now we have FPHELSIE. Twenty-five percent is definitely closer to the mark of the issues that we have to deal with.

One of the other things that no one has dealt with is funding for genetics professionals to actually deal with all the public that's going to want these services. There is no funding for training. We are losing geneticists. We are losing genetic counselors. We do not have minority recruitment of people to work with minority populations. I mean, there's not even a Native American genetic counselor. Why don't we have that? Because people do not fund those training programs. It's very expensive to be trained. You might as well become a doctor rather than a genetic counselor. You can make more money. We all work for very little money.

The other part is we need to train genetics people to work in public health departments. One-third of state genetics coordinators have training in genetics. Two-thirds of states have state genetics coordinators who report they have no formal training in genetics. How can that be? They're running the state genetics program.

Also, primary care providers don't want another education in genetics. They're too busy taking care of patients, trying to see enough patients to make a living. They want the resource people to be able to contact, and if we don't pay to train resource people, we're not going to have those primary care providers that want to provide genetic services to their patients. So I just want to make sure that the money is there for training and for ELSI issues -- FPHELSIE issues.

DR. WILLARD: Julio, and then Joseph.

DR. LICINIO: Just to echo what you just said and expand it even further in terms of the amount, I think that for the Human Genome Project the 5 percent was perfectly appropriate. I think it was actually a very visionary thing to have done at that time, because it wouldn't necessarily have to be done, and it was done, and I think it's really enriched the whole project.

But we're talking here about a very different ball game. For health care, in the example that Sharon gave earlier about the asthma studies, I do depression studies myself in a minority population. It is feasible to go and treat the people as you're doing the study and to offer -- like you said you buy a vacuum cleaner if you have asthma, et cetera. You're talking about very limited interventions over a very limited time course, and here we are proposing a long-term follow-up. In health care, it's extraordinarily expensive. It's not going to be 5 or 15 or 20. Maybe 200 percent, maybe 500 percent of the budget.

If you think about it, let's say, for General Motors, their biggest expenditure is not metal for the cars or anything to do with the cars. It's health care for the employees, by far. Recently they were able to change it to increase the deductible a little bit, and they're going to save several billion dollars over time, and their shares went up because of that. But it's an enormous expenditure.

So if you're going to have a very large project with a substantial minority of people that are uninsured, to provide health care for these people over time is going to be extremely costly. I mean, one idea could be that everybody who is in the project gets Medicaid

automatically, so they're not just dying as you watch them get sicker and sicker. But then if you do that, does that become coercive if you're poor, because if you do, you get Medicaid, but if you choose not to, you don't get it?

So it's a very difficult issue, and I think the ethics of following people up without offering adequate health care, and the cost of that has to really be dealt with very up-front and very clearly, with both ethicists and health economists, and that should be included in the project at the very beginning. Otherwise it's going to become very ethically problematic.

DR. WILLARD: Joseph?

DR. TELFAIR: I appreciate, actually, Kevin's recommendation, because it makes a lot of sense. If you stop and think about this and what's been said afterwards, I would actually draw people's attention to the Institute of Medicine's recent report on the public health infrastructure. They actually outline very well this disintegration everybody is talking about in that report, particularly some of the things that have been said earlier, and it gives a very concrete, a very well done outline of pulling this information together. So I just wanted to add that to that.

The second thing is that I also have an appreciation of what's being done in Dr. Collins' shop with a lot of different groups in terms of bringing constituent groups together to begin to tackle the issue of bridging between the bench scientists and the social and behavioral scientists on a lot of issues, particularly one of the ones that our group was participating in was on sickle cell disease and looking at ELSI issues related to that and bridging the work that was done, and it was very well put together, very well done, and also tackled over a three-day period a lot of these issues and came up with some very strong recommendations. So in terms of models of pulling this together, there are models that I think this group can really amend to the things that we're considering as part of our committee. So I just wanted to add that.

DR. WILLARD: Julio?

DR. LICINIO: One additional comment is that since this issue, I don't think it's going to go away, we could also think of alternative strategies. For example, if you're going to follow people over time to see outcomes, you have to wait a long time to see some meaningful outcomes on a population level in young people. In older people, those outcomes are going to happen much faster. So yes, you'd lose a lot of diseases of childhood, adolescence or early adulthood, but if you want to do a project like this in everybody over 65, for example, everybody would have Medicare, and then you jump a huge barrier in terms of following the uninsured, and you have the outcomes faster. I mean, you lose something, but at least the issues are not there.

So I think every possible alternative should be thought about because maybe including only people who have some type of universal type of care, veterans or people over 65 or something, might be a very plausible strategy.

DR. MARCHASE: Without in any way trying to speak against the idea that a public health concern should be important here, I think we have to remember Heisenberg's uncertainty principle, and that is that when you intervene in a system, if you perturb a system, you're going to affect the outcome of that variable. If the study is going to be designed in such a way that the public health of the participants becomes something that is treated, it will disenfranchise people that are not treated in some ways.

DR. WILLARD: Francis?

DR. COLLINS: I think a point about what the obligation is of research to provide medical benefits is a critical one, but it is not a new one for this project. There's a large body of ethical debate and literature about this, because I think you could argue quite strongly that it is unethical to carry out research that does not offer research opportunities to people who don't currently have health coverage, because in that process you may be neglecting important public health problems and not providing the kind of opportunity for participation which sometimes can be beneficial.

So it always comes down to this sort of difficult decision about what is an appropriate kind of benefit that you offer to those who participate in research that is not coercive but is also benevolent and generous. Again, in the debate that we had about this over a year or so, it was clear that you would intend for all participants to give back immediate information about data that's collected as part of the examination, both the physical exam and the laboratory exam, and that some limited additional medical benefits ought to be considered but would need to have very careful debate about just how far you could go. Again, both for cost reasons and for coercion reasons, I'm not sure that most of the people who have looked at this issue would agree that you can offer full medical coverage to the currently uninsured in a project of this sort.

But again, we should look carefully at all of those discussions that have gone on in terms of studying diseases in the uninsured, and there's lots of studies that have had to deal with that. Of course, this quickly gets into international research as well, in terms of what are your obligations to give medical benefits to people in developing countries, where nobody has much of what we would consider to be reasonable medical benefits, and yet we're asking them to participate in research.

DR. WILLARD: Debra?

DR. LEONARD: Well, part of this coercion aspect is controlling it. I noticed that in the report, you say that institutionalized persons' long-term mental health or custodial care individuals would not be included in the study. I understand why that's done, but it also concerns me that one of the issues of mental illness that isn't really appreciated broadly as an illness as opposed to something you could control are being excluded from the possibility of furthering the genetic understanding of mental illness by this exclusion. I don't know if there's some way to get around that from an ethical perspective, but it is a bit concerning.

DR. COLLINS: Yes, I agree, and that was not an easy kind of discussion. Again, I think the consent issues dominated that part of the discussion, how could you really get adequate consent in that circumstance, and people were uncomfortable with the sense that that would be meaningful. That was the main reason for --

DR. LEONARD: But it couldn't be from a family member or guardian or someone who could provide that? Basically, you're not allowing that family to benefit from the potential of giving their consent that this person could reasonably have at least samples taken or something.

DR. COLLINS: I think that's entirely open for further discussion.

DR. WILLARD: We're drawing to a close here for this session. I want to take my prerogative to ask the last question. I want to address it to Francis.

Francis, in your role as director of NHGRI, it's easy for us to forget the fact that the reason you're sitting around this table is that you're actually representing NIH, not NHGRI specifically. So I want to ask you, during the past year or so, as thoughts of this large

population study have been developing, to what extent you have had interest or positive feedback on the part of your director colleagues, and whether this is truly something which is, at least at the current stage, receiving broad, pan-NIH support.

DR. COLLINS: It's a very appropriate question. This project has been presented to all of the institute directors on a couple of occasions, and there have been numerous conversations with specific institutes, particularly those that have very large investments in this kind of research, like the Cancer Institute, the Heart Lung and Blood Institute, and so on. Just to summarize what has been a very diverse set of discussions and opinions, I think it would be fair to say, and I think my institute colleagues would be comfortable with this kind of summary, that there is a lot of enthusiasm for the potential scientifically of what a study of this sort could tell us about the relationship of genes and environment and disease, a lot of recognition that a study of this sort would contribute the kind of data that would shine a light into many different corners of our current ignorance, a deep concern about the cost and whether, in fact, this is something that could be mounted in the current budget climate without additional funds, as we talked about earlier.

I don't think there would be any institute director around who would say that this is something that we could mount right now. But I have not discerned any major scientific disagreements with the statement that this would be an increasingly valuable resource as we try to learn more and more about how all of our discoveries about genes and environment could apply to public health, and it would have many spinoffs in terms of things like nested case/control studies that would come out of this that would provide the grist for a lot of other research that would go on.

Many of the NIH institutes, if this particular study was already going on, would look at their portfolio and realize there are other things that they're currently paying a lot for that could perhaps be done more efficiently through a coordinated national study of this sort.

DR. WILLARD: Thank you for that.

With that, the morning part of this session will come to a close. I want to thank Dr. Kardia and Dr. Marchase for their comments, and Dr. Fink, although he's long gone, for his. I think we've touched on a lot of important points that the committee will have to consider over the remaining course of this day and then beyond, and I thank you for your participation.

We'll now move on to a public comments period for this meeting. One of our critical functions is to serve as a public forum for deliberations on a broad range of human health and societal issues raised by the development and the use of genetic technologies. So we greatly value the input that we receive from the public at large.

We set aside time each day to hear from members of the public, and we both welcome and appreciate the views they share with us. In the interest of our full schedule, I'd ask the two scheduled commenters to keep their remarks to five minutes, if possible.

So today we're going to first hear from Kathleen Rand Reed, representing the Rand Reed Group.

Welcome. Maybe you can find a chair at that end.

MS. REED: Good morning. I am an applied biocultural anthropologist and ethnomarketer. Today's presentations, roundtable discussions and program segments cover broad topics, as large population studies and their subfocus on the scientific community, public engagements and bioethics. Tomorrow will cover genetic discrimination and

pharmacogenomics. I won't be here, so I tried to bring to this forum policy perspectives, information and mechanisms that relate to the efficacy of all aspects of this meeting, and they are specifically, one, the need for inclusion of an outreach marketing to the 18- to 34-year-old hip-hop, rap and hurban, or Hispanic urban generation for clinical research and genetic educational information; two, the need to create a firewall between health and disease-oriented genetic and clinical research and the use of DNA analysis within the law enforcement realm, specifically CODIS, the FBI Combined DNA Index System; and three, the need for outreach to the pre-migration communities, families, and relatives, incorporating transnationality within the genetic educational models.

I bring this up, and I just wanted to be very quick about this, because I'm very much involved in that community, and especially I serve on an IRB with Heart, Lung, Blood. One of the things I notice is that when people are doing outreach to many of the minority communities, they tend to go to faith-based organizations and churches, et cetera. But given that the rap and hip-hop culture emerged out of the 1970s, we're talking about a popular culture and a cohort that has actually, in many cases, grown up over these last 30 to 35 years. Yet when you look at clinical research and you look at the marketing, and especially when you're talking about the new group in terms of starting families and genetic education, they're almost missing in action.

By the way, there's a lot of fear on the part of people to do outreach in this because historically this has been stigmatized, and it's been linked with crime, violence, and crude thug life. But today, the culture has segmented to the point now where you even have Evangelical aspects called Christian hip-hop. So it's a popular culture international segment of a cohort population that, quite frankly, given the other things that are going on, are just not being served.

The Latino aged 14 to 24 group that comprises more than 20 percent of the Hispanic markets in their new identity, they're now considered pan-Latin in their identity, and they often speak with a fusion of Spanish and English, and many have never visited their parents' country of origin, and yet they're an intricate part of this culture. We don't have to talk about the growth of the Latino and Hispanic population. It was 35.6 million in 2005 that are now 41.3 million, and that's the legal side of the house. So I would recommend that a representative advisor to this committee for this market and this cultural lifestyle for input and reality checks on the effects of these discussions and decisions in this segment.

The second part, real quick, facts on the ground. Let me give you six points.

Number one, in 2003, North Carolina technicians compared DNA left from a crime scene with genetic profiles in the state's database of convicted felons. The crime scene DNA did not match any of the 40,000 felons on file, but since it was remarkably similar to an inmate, the technicians concluded that the unknown man was from the same parents as the inmate.

Florida's DNA database operators have been permitted to give investigators the names of convicted offenders who match a crime scene sample at 21 of 26 alleles. It has been estimated that men who have 21 alleles in common are almost always brothers.

African American males are more than 12 times more likely to be arrested and not convicted than whites, and yet a growing number of jurisdictions are collecting genetic information from arrestees not convicted, and the materials are not destroyed upon establishing the innocence of the arrested person.

Many African American and Latino communities and zip codes are hyper-segregated, to the point of 99 percent, and a growing number of children born in these hyper-segregated communities share known and unknown male parentage, and in some cases are half-siblings.

The reason I'm very much involved in looking at the establishment of a DNA database is for the reunification of Katrina families and children. One of the barriers I'm running into is that because there's no firewall between the CODIS and the law enforcement side of the house and the communities where this word has spread and there's great fear, many people have not come forward to even discuss it because many people in many of these hyper-segregated communities are terrified of the genetic side of the house. So this is an issue that has real effects in the reunification of many of these families that have been separated tragically with Katrina.

So the recommendation would be to investigate the use and abuse of the genetic familial searches, which is really what it's about, and we're dealing with that in terms of anonymizing samples, et cetera, and this being an ethical issue, and the development of a policy position which creates this firewall between the health and disease-oriented genetic and clinical research and the use of DNA analysis within the law enforcement realm; and lastly, develop policy that establishes the destruction of physical samples used in DNA testing.

The very last, which will take less than 30 seconds, is the need to incorporate transnationality within the genetic educational models; in other words, pluralist bioethics. Many discussions about outreach for genetic education to minorities especially, genetic sampling and family histories, still center on native African Americans and, to some extent, the Hispanic population. However, one of the biases incorporated within those discussions and policies is the lack of understanding of the dynamics of transnationalism, transnationalism being the ease with which immigrants live in the United States but support relatives, run businesses and participate in a two-way exchange of gifts, commodities and cultural practices in both the United States and the country of origin.

In the development of policies and mechanisms for genetics, health and the U.S. society, certain aspects of transnationality must be taken into account. One which is critical is the outreach to not only the U.S. communities but the pre-migration communities, families and other persons who act as family or fictive kin, to the residents in the United States, and to provide the U.S. residents with information developed for their pre-migration communities and family members. It increases not only the efficacy and effectiveness of the outreach but often augments from a cultural perspective the underlying tenets of informed consent. There are people who will, before they give you family information, call grandma or compadres and ask them should they, and if they say no, then they will come back to the researcher and say thank you very much and be very loving and very nice, but they will say no.

So if this pre-migration information can be provided to the families and, in the case of many Latino families, the godparents, you may see the efficacy and the effectiveness of the sampling go up.

Thank you very much for your time. Are there any questions?

(No response.)

MS. BERRY: Thank you very much.

Next is Joann Boughman, American Society of Human Genetics.

DR. BOUGHMAN: Good morning. On behalf of the American Society of

Human Genetics, and as its executive vice president, we thought it appropriate that we make some comments on the proposed large cohort study. I'd like to thank Dick Marchase as representative of FASEB, an organization in which we are members, that I think he has addressed some of the broad issues extremely well, but we would like to make just a few comments.

The need for large-scale population studies to understand genetic and environmental factors that are involved in the relationship to disease is certainly evident to those of us in the fields of human genetics, medical genetics and genomics. The design, implementation and analysis of such comprehensive studies are obviously, as we've heard many times over, of enormous complexity.

As with any group of scientists, the human genetics community does not speak with a unified voice on the promise of such studies or on the priorities that should be assigned to them. The leadership of ASHG has discussed many aspects of this proposed population cohort study. While there is widespread and general support for the concept, as expected, there are some diverse views -- the devil is always in the details -- on the manner in which the study would be implemented, the nature of the data collected, and the extent to which the data will translate into the promise of treatment or prevention.

ASHG applauds the NHGRI convening working groups and gathering comments from many in the scientific community, both inside the NIH and in the extramural community, and we also commend SACGHS and others for continuing this dialogue. The gaining of interest and communication among the scientists will be enhanced by every one of these dialogues that we have.

The design of the study, including ascertainment of systematic data, structured collection of variables, and quality-controlled data analysis, should be of enormous benefit. Nevertheless, it is clear that the design of this study is an immense challenge because the specific aims will necessarily evolve with time. In contrast to the Human Genome Project, as we've heard, which had a specific and defined endpoint, in the case of this cohort study, the good news and the bad news, if you will, is that the goals must be broad, and many specifics cannot yet be defined, and the data gathered would need to be broad enough so that yet undefined or currently unrecognized questions could eventually be asked and answered.

The strong interest and general support for the large population cohort study derived from the widely held conviction in our community that such a rich data set should have important clinical implications that we hope can be translated into general benefit, and the hope is underlined there as you all have discussed earlier this morning. That is one of the challenges, is the translation of the results of such a study into action in clinical practice.

We see the challenges proposed to the study coming in at least four forms, and in some respects this becomes a summary of this morning's comments. Would or do existing data sets have sufficient breadth and depth to provide at least some of the information as proposed in this study, and if not, are there ways that the existing data can be further mined to limit the costs of the cohort study? In the written remarks I've listed a few, but a few others have been named this morning, including the Framingham Study, the Children's Study, NHANES, and the Veterans Study. Are there ways that we could further mine some of those data sets to ask new or better questions?

The second point is a major one. Given the current fractious state of health care in the U.S., can a truly coherent cohort study be designed, data collected and analyzed, and

benefit returned to the participants and others in the U.S., at a reasonable cost? For example, it is proposed that information will be collected from medical records, a daunting challenge, as we might expect. Or would the health care system itself have to be revolutionized to benefit from such a study?

Many in the genetics community wonder if such a systematic study can be carried out in a way that can be fully utilized in the United States. In our patchwork system, absent systematic electronic medical records and any realistic vision of a uniform or universal delivery of health care, the direct applicability of the results to the broader community must be appropriately questioned. In other health care systems around the world, the implications of study results could be more quickly, efficiently and effectively utilized, integrating the results of a well designed study into the point of practice much more directly. That doesn't mean this shouldn't be done. It just might be done quicker and more effectively elsewhere.

In contrast to the Human Genome Project, which required a development -- and I'm amazed that these were the terms that my colleagues used -- which required development of relatively inexpensive high-throughput data sequencing and computational tools to assemble, compare and analyze digital data, the cohort study demands the identification of a population that has sufficient breadth and depth to allow analysis of a myriad of relevant questions, the identification of numerous biological variables to be measured, and their tabulation, and the creation of robust assessment and computational tools to define, measure, and assess the effects of environmental changes over time. Compared to the Human Genome Project, these perceived requirements are far more complex.

Fourthly, as spoken about by Dr. Marchase, the costs of the project will have to come from funds outside the usual funding mechanisms as they are likely to be so large that the effect on usual biomedical research funding could be highly deleterious or even devastating. It is therefore anticipated that this study could not and would not directly deter or redirect the current limited biomedical basic research funding.

Finally, as recognized by others, the choice of individuals and populations to be included, and their relative representation, is far more complex in our highly heterogeneous society here in the States, and the need for the diversity, and the manner in which that diversity is handled, need to be carefully considered prior to the identification of those to be actually included in the study. The many issues related to recruitment, ascertainment, fully informed consent and privacy will be more directly addressed by others but remain in the forefront and concerns of the human genetics research community.

Our researchers and clinicians have been consistently in the lead on addressing and discussing openly ethical, legal and social implications of our own research, and we maintain that this endeavor, along with the educational issues, are of the utmost importance.

As an organization, ASHG generally supports this concept and recognizes the importance that results of the proposed study would provide to all of us. We encourage individual members of our organization to remain active in the process of the design and the development of this proposal, and today we'd like to again commend the SACGHS on the development of timely and important questions to consider in the analysis of this proposal and bringing them to the public, and support your effort to analyze this proposal in detail.

Thank you.

MS. BERRY: Thank you, Dr. Boughman, and Dr. Rand Reed both for your comments and your input. We'll certainly take all of those comments into account as we

proceed.

At this time I'd like to return to the Chair's introductory remarks, those that we glossed over when we first began in the interest of everyone else's schedule, and talk a little bit about the work that the ex officio agencies are up to in order to enhance SACGHS' currency and ability to stay abreast of developments. In August, you might recall that Dr. Tuckson asked the ex officios to provide us with updates on the relevant activities in their agencies and departments, and these updates, as was mentioned earlier, can be found at Tab 3 of the briefing books. Our thanks go out to the ex officios for reporting to us about these developments. The information will be very, very useful, and it's relevant to our work.

I know that in requesting these updates, Reed was hopeful that they would also be a resource to each of you by increasing your awareness of relevant activities across the agencies, and perhaps revealing opportunities for more interagency collaboration.

Now I'd like to take a few moments to highlight several of the agency initiatives. You may recall that at our meeting in October of last year, we learned about the Surgeon General's Family Health Initiative. The Family Health Initiative is a transdepartmental program aimed at increasing public awareness of the importance of family history and health, and providing the public with tools to be able to gather, understand, evaluate and use family history to improve individual health.

The Family Health Initiative is gearing up for its second big national event this coming Thanksgiving Day. We wish the Surgeon General and all the agencies involved in supporting this important health promotion message great success again this year, and we look forward to hearing how it all goes.

A few weeks ago, AHRQ sponsored an important meeting on gene-based discoveries. The agency's goal was to identify knowledge gaps and barriers to the clinical use of gene-based discoveries and develop strategies for overcoming the barriers and improving coordination of relevant federal activities.

Dr. Chesley, could you tell us a little bit more about the meeting and outcomes?

DR. CHESLEY: Sure, I'd be happy to. On behalf of Dr. Clancy, Dr. Goopernick convened this conference, whose objectives you mentioned. The title, though, is one important thing I do want to mention. It was titled "Genomics and Medicine I," and it really was titled that way to reflect the reality that we saw that as a first dialogue in an ongoing conversation both with our partners within the Department as well as key experts outside of the Department. The conference included representatives from across the Department, FDA, CMS, NIH, HRSA, as well as others.

The first day of the conference focused on genomics, and the second day focused on pharmacogenetics. I think it's important to point out that we'll have a detailed summary by mid-November, we hope, and that, of course, we can make available to this group.

One of the things that I think was key during the discussion and during the meeting is sort of pointing out some gaps between what we know and how we can use that information. One of the things we were looking for at AHRQ, as well as with our collaborators across the Department, is how to build on some synergies that may exist in AHRQ programs, such as our HIT program. We, for example, talked today about the need for an electronic medical record in the context of the study we were talking about this morning. So whether or not there's a role to develop or facilitate such an electronic medical record was one of the things

that we chatted about in our conference.

But also the intersection between, or I should say with, some of the evidence-based programs that AHRQ sponsors, like the EPC program, and others.

One of the things that I think was a key point made during the discussion by participants was their interest in having methods workshops and conferences to discuss issues involved in linking the information and data sets, both from genetic lab tests as well as clinical databases, in order to do research in this area.

MS. BERRY: Thank you very much. Appreciate it.

At our February meeting, we heard from Dr. Steve Groft, director of the NIH Office of Rare Diseases, and Dr. Joe Boone from CDC, about plans for a national conference on access to quality testing for rare diseases. The conference was held last month.

Dr. Groft, perhaps if you could come forward and give us a brief report on the outcomes of the meeting. Thank you.

DR. GROFT: Good morning and thank you for the opportunity to come back and report to you on what I felt was a very enlightening meeting with quite a bit of participation. We had over 150 registrants for the meeting representing clinical geneticists, patient advocacy groups, patients themselves, the clinical laboratories, federal government employees and program officials, and the professional organizations.

I think we tried to focus on a number of different areas, including infrastructure, current models for test translation from the research laboratories to clinical applications. We also looked at quality assurance and quality control measures, including the international aspect of test flow and sample flow. A major focus was on the need for educational efforts to assure and promote quality in patient testing and in the test translation process. So it was a rather busy couple of days and couple of evenings as we started, and some of the outcomes -- you've received, I think, a copy of the set program, the Collaboration, Education, and Test Translation Program. I think that was provided to you. You got that okay?

That's something that is under development, and we hope to have it implemented and open for business by January of 2006. Dr. Giovanna Spinella, Andy Faucett, Dr. Bonnie Pagan, Dr. Susanne Hart from Human Genome were involved in developing this, and we'll be going through processes that are identified there in the description of the project, and we hope to start to stimulate the development of genetic tests for the rare diseases. I think four or five years ago the feeling was that nothing much could be done, there wasn't much interest in the rare genetics disorders. I think by the last two meetings that we had, the first one in Atlanta and then here in Washington, there is considerable interest. It's just a matter of bringing the people together, focusing on the issues and the concerns and the needs, and then having individuals who are committed to finding answers work together to get things moving, and I think we've been able to do that.

As all good groups, you always want room for another meeting, so we are planning another meeting in 2006. I don't think we can get away from that. But there are going to be presentations at the American Society of Human Genetics and the American College of Medical Genetics. We are distributing the results and the findings and looking for more input from different people as we go along.

Another recommendation related to education, we felt an awareness campaign about genetic testing and genetic counseling services was necessary here in the country. There just seems to be a tremendous absence of adequate information to the public, to

clinicians, to the researchers about the requirements and the needs related to genetic testing. So I think we'll be focusing on that however we can with whatever partners we can gain as we move forward.

There's considerable effort already devoted to development of international quality assurance and quality control guidelines, and I think that will continue. The OECD group from Europe and others, Joe Boone is intimately involved in this, and we will continue working that area and just facilitate the development of the genetic test across borders.

Currently, the focus has been on molecular DNA-based tests, and we're hoping to expand or consider the development of new and expanding networks to focus on the biochemical and cytogenetic procedures for the development of genetic tests. I think it was two groups that sort of felt that maybe they were on the periphery, but after the last meeting a feeling of inclusion I think is there, and we're hoping that they either will form new networks or we'll just incorporate them into the existing network.

We base many of our proposed activities for the set program on activities that Dr. Bill Gall, the clinical director from the Human Genome Research Institute, has been involved with in developing genetic tests. We use that as a model or pilot to see if we really could utilize commercial laboratories, academic laboratories to develop genetic tests. During the past two years we've developed 21 or 22 different genetic tests. We're using this as a model.

So we'd like to extend this a little further to see if we can really expand this out into the community further and a couple of years from now see what the possibilities are for maybe a little bit larger initiative throughout the entire NIH structure.

So what's about it. Do you have any questions? There are some more qualified people in the audience who were there than I am that can answer questions. But if you have any questions, we'll try to answer them.

MS. BERRY: Thank you so much, Dr. Groft. Appreciate it.

Next I'll attempt to report on the activities of several SACGHS members and staff, folks who have been up to some very interesting things, and I'll start with Dr. Telfair who, as you know, is the SACGHS liaison to the HHS Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children.

What is the acronym? How do you pronounce that?

DR. TELFAIR: I'm only a liaison.

(Laughter.)

MS. BERRY: All right. Well, the committee held its fifth meeting in July, and we'd be interested to hear a brief update as to what transpired at that time.

DR. TELFAIR: Well, in the packet is a summary, a condensed version of a much larger report. So I will highlight a few things, just the bolded parts of this report. So there's much more discussion there.

This is a committee where the last meeting I went to was their fifth meeting, and actually this week is their sixth meeting. So they've been very active, and their primary focus is on newborns and childhood. The committee began its deliberations as a long-term follow-up for discussions with the public comment review from the American College of American Genetics report on newborn screening. The report itself was "Newborn Screening: Toward a Uniform Screening Panel and System." The notes from that and what proceeded on that is in the handout, but just three things that I want to highlight.

The focus was on the issue of improved access to services, especially to

underserved and the most vulnerable populations. The other one was to ensure services of high quality, particularly those that have a high level of scientific merit. The other aspect of that was also to begin to look at issues related to culturally competent care. This includes things like health literacy and giving consideration to parents who have to make treatment decisions. The committee itself reviewed a very large number of public comments that came in. The public was given about a two-month time period to review the document, which they could get access to through websites and other means, and then to provide comments.

I forgot in my report to sort of research the actual number, but Dr. Mike Watson is here, and I'm sure he could tell you how many comments they got. So I would leave it up to that.

The committee itself actually had other business that it dealt with. It is because of its relationship with HRSA, and within HRSA it is the Maternal and Child Health Bureau. So Dr. Peter van Dyck, who is the associate HRSA administrator over that unit, has a high degree of responsibility and interaction with that group, and Dr. Michele Puryear, who is the director of the Genetic Services Branch, was within the DHHS, HRSA, Maternal Child Health Bureau, is in charge of that. So not being a fed, I have to get used to the acronyms.

But anyway, within that group, a major focus was on the issue of screening, and Dr. van Dyck's primary comment in his role was to discuss with the committee a means by which a letter will be drawn that will go to Secretary Leavitt, but at the same time how the Maternal and Child Health Bureau will be involved in communicating the information from that, and also looking at the recommendations from that particular study. I would encourage everyone to really review that report if they have not already done so, to look at that report.

Dr. Brad Therrell meets with this group, and Dr. Brad Therrell is the director of the National Newborn Screening and Genetic Resource Centers, and their main responsibility is basically to work with states to track the activities that the state health directors were involved with newborn screening there. Then the report, I refer everyone to the two handouts that he gave, which basically updates the status of the newborn screening at the states, both the number of conditions as well as the number of states that will do universal newborn screening in key areas. Also, he provides in great detail a detailed map to look at that as well.

There was an issue that came up in prior meetings related to the role of evidence and other factors that influence evidence in relationship to public policy decisionmaking, and several scientists were asked to come and give presentations on those, and those are listed in the report as well.

Then there are several subcommittees that exist within the committee itself, and those committees are Education and Training Subcommittee that was led by Dr. Jennifer Howse, but now someone else will take over that role because her time on the committee ended; Follow-Up and Treatment Subcommittee; and a subcommittee that deals with laboratory standards and procedures.

Then there's a public comment period always, and I list a large number of the persons allowed to do public comment, but there was also a relationship with the American College of Obstetrics and Gynecology, which was given a little bit of time to discuss their perspectives on the ACMG report.

I tried to be brief.

MS. BERRY: Thank you very much, Joseph. Appreciate it.

Dr. Leonard is up next. She was recently appointed to serve as our liaison to

the CDC EGAPP Working Group and just came from a meeting of that group and can provide us with a report on the meeting and the group's progress.

DR. LEONARD: Well, Muin, please feel free to jump in here because I feel like I'm usurping what has been done by you and Linda Bradley.

EGAPP is now a year old, so a steering committee selected a working group of 13 individuals. Al Berg is chair of that working group, and the working group has had three meetings to date. In addition, there are subcommittees of the EGAPP Working Group that are working on various subprojects of EGAPP. So overall, just to bring everybody up to speed who may not know what EGAPP is, it's Evaluation of Genetics in Principle and Practice. Is that right? What is it?

(Laughter.)

DR. KHOURY: Evaluation of Genomic Applications in Practice and Prevention, double P.

DR. LEONARD: Practice and Prevention, okay. But you must have somebody who stays up like all night designing logos for you, because I was very impressed by the logo with the big E, and then G-A-P, and then a big P, with a DNA going between evidence and practice. I mean, who came up with that?

DR. KHOURY: We love to do this in the government.

(Laughter.)

DR. LEONARD: Francis, maybe you need a percentage of your budget for logos.

(Laughter.)

DR. COLLINS: It always results in a war between the staff. So you also have to put in some money for employee counseling.

(Laughter.)

DR. LEONARD: Sorry. I shouldn't have gotten sidetracked there, but it was quite impressive.

So the working group has spent time developing methodologies because they are approaching evaluation of genetic applications in a different way than some of the more stringent groups, and it's really delightful to see them considering some of the more social and knowledge-based aspects rather than strictly defining utility or benefit based on medical treatment availability. So they have developed an entire process, a process for selecting the genetic applications that they want to evaluate. So there was a whole group on how you choose these and prioritize them.

Then there's a request for task order, RFTO -- it's like an RFP -- that goes out to evidence-based review centers requesting them to do an evidence-based review on the particular topic that's been selected by the working group. Then there's a whole description of what is needed, and the evidence-based review center will provide that evidence-based review back to the committee in a specified amount of time. That working group will then take that evidence-based review, which will have its own conclusions, but the working group will then make recommendations based on that evidence-based review.

The recommendations. They are now developing how they are going to make these recommendations, and they realize that the recommendations have implications for physicians, as well as for individuals and how they tailor the needs of those different groups. So they're being very, very thoughtful about this entire process.

So they're looking at the benefits in terms of medical benefits, diagnosis/prognosis/treatment options, patient benefits, both medical and personal, family benefits, societal benefits, and public health benefits. So they are being very broad in the range of benefits that they're looking at.

So there are two evidence-based reviews that are far enough along that I think I can mention the specific topics. The first has gone out for request for task order, and I believe at this point the specific evidence-based review center has been selected, and that one is looking at cytochrome P450 testing for patients with depression who are being treated on SSRIs, either prior to or on treatment for SSRIs. That one will have a nine-month review process for the evidence-based review to be completed, and that will then come back to the working group.

The second topic is HNPCC testing algorithm from screening by Bethesda Criterion Family History through screening testing by MSI and immunohistochemistry to full gene screening for those that are positive, this entire algorithm. So since this testing is more complex -- and this would be for patients with newly diagnosed colon cancer. Since this is a more complex testing algorithm, there's a 13-month time frame being given for this, and this is about to go out for a request for task order response from the evidence-based centers.

Finally, the working group is considering if they can do fast-track options. The two that I mentioned are full-blown evidence-based reviews, but they're considering the possibility of fast-track topics when they want a narrower evidence-based review or if there's a much more limited amount of literature, and they're having discussions about how to do these. But those would be more on a time frame of three or four months.

So it's very exciting to be a liaison to this group. I think they're doing some really good things and definitely thinking outside the usual evidence-based review box.

MS. BERRY: Thank you, Debra.

DR. LEONARD: And since the meeting was Monday and Tuesday, you'll get my report later.

MS. BERRY: Okay. It's in the mail.

I also want to take note of an interesting policy research project being carried out in the U.K. on the evaluation of clinical genetic testing for complex conditions. The Wellcome Trust is funding the project, and scholars from Cambridge and Exeter Universities are leading the project. Last month the project team carried out focus groups with a number of U.S. experts to gather perspectives about how genetic tests can be evaluated before entering routine clinical practice, and how regulatory and health care systems can ensure the availability of valid clinical information for the interpretation of genetic test results.

Emily Winn-Deen participated in the consultation, as did a number of ex officio agencies.

Emily, could you give us a brief summary of how the focus groups went?

DR. WINN-DEEN: Yes. I'm not really in a position to summarize the focus groups because these were designed as a series of focus groups where each individual subgroup didn't really have access to what happened at the others. I think maybe Stuart would be a much better person to give a summary since he sort of ran all the focus groups.

I can say that in the focus group that I participated in, we raised a number of questions without coming to any clear answers, and part of what the group running this focus group was trying to do was to pull together the common threads and what things are common

threads across both the U.S. and the U.K., other countries, what things are unique to a country like the U.S. that has diversified health care as opposed to nationalized health care.

So if you don't mind, I'd rather let Stuart give a little overview, if you don't mind.

MS. BERRY: Stuart, would you like to, or do you want to defer?

MR. HOGARTH: I must admit, I didn't come prepared to give a summary of our work in the focus groups.

DR. WINN-DEEN: Can you talk into a microphone and just give a little overview of what the point of it was and where you are in the process?

MR. HOGARTH: Yes. First of all, thank you very much to Sarah and Amanda for inviting me to the meeting. As I say, I hadn't come prepared to talk about the research, but it's a three-year project, and we are talking to all the stakeholders who have an interest in the evaluation of clinical genetic testing. So that's the government agencies, health technology assessment, regulators, clinicians, patient groups, and also industry.

We've run two focus groups in D.C. last month, and we had some really stimulating discussions with very diverse set of perspectives from those stakeholders. We're about to run out to U.K. Europe focus groups, which will be very interesting because we'll really start to see the differences in how the health care system structures and the different regulatory environments -- I mean, the way these issues are addressed is very different in Europe and the U.S.

I've just come back from Canada where I've been speaking to people there to try to get a take on that country's approach to these problems, as well.

What I would say at this stage is that coming out of the two U.S. focus groups, there was a very strong discussion about infrastructure issues around the need for translational research and the lack of support for getting basic research findings through into clinical practice, and how there might be some kind of need for a change to the whole infrastructure where all the different points of control, the different gatekeepers involved, whether that's people in the reimbursement side, whether it's people in the regulatory side, whether indeed it's the professional bodies, which have a very important role to play in terms of clinical guidelines, can somehow actually be coordinated. That idea of actually coordinating the activities of different groups is, I think, a crucial one.

Aside from that, I think I'd probably stop rambling on, actually. Thanks.

DR. WINN-DEEN: Thank you, Stuart. Thank you for doing a much better job summarizing it than I could have from just one slice of the pie.

I think that the one thing that I just want to point out is that what Stuart made as one of his last points there, about the need for coordination, is something that our committee has also identified. So I think that's one thing that we should continue to have as an underlying theme for all of our deliberations on whatever topic, that we just need to continue to push for coordination, at least among the HHS agencies for whom we can advise formally.

MS. BERRY: And just to clarify, Emily, you participated as an individual, in your individual capacity.

DR. WINN-DEEN: I participated as a member of the diagnostics IVD assay community. So it wasn't as an officio or ex officio or representative of SACGHS.

MS. BERRY: One more item before the magic hour begins. In September, at the Western States Regional Genetic Summit, Suzanne Goodwin, our very own, gave a

presentation on the SACGHS coverage and reimbursement report, and the summit was organized by Sylvia Au and colleagues at the Hawaii Department of Health. I wanted to make sure that we recognized that work and that summit.

There are other activities that we're going to talk about, and rather than going through all of them now, this relates to Reed's custom of putting up our priorities chart and seeing where we are, where we've been, we'll defer that until after lunch. So there is more work to talk about.

For committee members and ex officios, the lunches you ordered will be brought here. For members of the public, lunch is available in the hotel restaurant, as well as a number of nearby restaurants.

We will reconvene -- shall we say 1:05? -- 1:05, to give everyone a full hour.

(Whereupon, at 12:05 p.m., the meeting was recessed for lunch, to reconvene at 1:05 p.m.

AFTERNOON SESSION (1:08 p.m.)

MS. BERRY: Let's get started. We will dispense with the chart, the Reed Tuckson chart, but I will highlight just a few key points, and that is some folks have mentioned the coverage and reimbursement report that we worked on at the last meeting. That is being finalized. Staff had some additional editing recommendations. We anticipate having final activity on that and get the report out in short order. For members of the committee, there were some editorial recommendations. We'll get copies of those in redline tonight. I ask that everybody take a look at those, and tomorrow we will either go yea or nay. So we will either go back to the original version that we proposed or we will accept the staff recommendations for the editing changes, and we'll move the coverage and reimbursement report forward.

Another item I wanted to call to everyone's attention is the fact that the committee deferred consideration of the issue of gene patenting until the National Academy's Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions issues its report. That report is due out next month, November 9, and given its imminent release it might make sense for us to task a small group to review the report and provide us with some input about its recommendations and findings and whether there are issues this committee should take a look at.

I think, Debra, am I correct in assuming that you will graciously agree to head up a little working group for that purpose?

DR. LEONARD: Sure.

MS. BERRY: So anyone interested in volunteering to work with Dr. Leonard on the little, small work group and analyzing that report, see Debra, and that will move forward.

Another clean-up item. I wanted to draw to your attention a survey that's in the table folder. HHS would like feedback from members and ex officios about the effectiveness of the committee's activities. So we'd ask that you complete that survey and hand it to Abbe Smith at the registration desk before we adjourn.

Finally, I will turn everything over to Sarah Carr, who is going to give us kind of an update on what we should already know and be acting upon with regard to ethics

rules.

MS. CARR: Right, and in the interest of time, I'm not going to go through my usual reminders, because I know you all are very attentive to the conflict of interest rules. So I won't go through that, but because we're also going to hear about legislation tomorrow, you want to remember that you can't lobby while you're here.

I also want to just mention that in June I also sort of lectured you about the Emoluments Clause, and there's been a development since June. The Justice Department has issued a ruling that the Emoluments Clause will not apply or does not apply to certain special government employees. It's not across the board. It sort of depends on the nature of the committee that the SGE is serving on, but an analysis has been done of our committee, and the members of our committee are not subject to the Emoluments Clause unless you are on another committee. So if you're on another federal advisory committee, then don't assume you're not covered for that committee.

We'll be getting you more information about this as the implementation of this change, significant change, is carried out. But I did want to mention it because I had brought it up in June and because I know a number of you from time to time think about doing some work overseas.

Then the last thing I'll say is that there's still a form that you will probably have to fill out about this, so you're not totally off the hook. But anyway, thank you.

DR. WILLARD: Welcome back. We'll continue with our session on large population studies, and specifically now we're going to hear from four experts in the area of public engagement who will together make up a panel, who are waiting patiently at the head of the table. I think, from an organizational standpoint, we will not have questions following each presentation. So, committee members, if you can take notes and save them up, and then we'll have a panel discussion when all four speakers have completed their presentations.

So first we'll hear from Joan Scott. Joan is a certified genetic counselor with over 25 years of experience in clinical genetics, the biotech industry, and in genetic policy, and she's now the deputy director at the Genetics and Public Policy Center of Johns Hopkins University.

Joan, thank you for joining us.

MS. SCOTT: Thank you for the invitation. I elected to come up here so I could drive, not that I have a control issue or anything.

(Laughter.)

MS. SCOTT: So I appreciate the opportunity of coming to talk with you today about public engagement, to engage on this subject. I have divided my time into three areas. First of all, I'd like to spend just a couple of minutes talking about some general principles about public engagement, because we hear that term used a lot, and it can mean a lot of different things to a lot of different people, and there are many different levels at which you can engage the public. So I think to help inform our discussion later on, it would be useful to take a few minutes just to talk about what the universe of public engagement is. Then I'll talk about our experience with the genetic town halls and how information that we learn might inform a public engagement activity around large population studies; and then specifically the committee had some questions that they wanted me to address, and I'll close with those.

So first of all, just from a very basic perspective, what do we mean about public engagement? You can, as I say, engage the public at a lot of different levels. At the very

simplest end of the spectrum, you can simply want to inform or educate the public, and we heard this morning that that's a necessary thing to do. Some would argue as to whether or not that's really public engagement because you're not requiring much work on the part of your participants, except passive receptivity to the information. But nonetheless, in your overall strategy, that is one method where at times it will be an important component of your overall strategy.

It does, however, sort of imply that you've got a one-way communication going on, whereas a more consultative approach to public engagement assumes that the public brings to the issue and the topic some very valuable experiences and perspectives and values that will help inform your overall policy issue or whatever it is that you're consulting them about.

That said, however, again there are a lot of different levels at which you can engage the public. Doing surveys can help inform what the public thinks, knows and feels about a particular topic. Doing focus groups, moderated focus groups, will give you a little more nuanced understanding about what the public's attitudes about issues are and some of the values that shape those opinions. You can ask the public to do a little more work in looking at the issues through workshops or scenario development. In deliberative democracy, you provide an opportunity for your participants to learn more about the subject, hear from the experts, hear the different points of views discussed and debated, and then to deliberate about those issues. Then ultimately, you can ask them to do the ultimate work in actually coming to a consensus agreement about what the best policy option is.

So there's lots of different levels at which to engage the public. The one thing that's common about these particular approaches that I've discussed is that the issues identification and agenda-setting tends to rest within the hands of the organizers, whereas a more collaborative approach to public engagement invites the community, however you want to define that community that you're engaging, early on in the process in the issues identification, framing the issue, prioritizing what the issues are for that particular community, helping set the agenda for what those engagements are actually going to look like, helping devise outreach strategies within that engagement.

The farthest end of the spectrum can not only empower your participants to make the decision, you can agree to abide by the decision that they arrive at. Now, I suspect that's not going to be the method that will be chosen here, but you can do that.

So with that as a background, as I say, there's lots of different ways of engaging the public. So when you hear that term, it can mean a lot of different things depending on what your ultimate goals are for the engagement, where you are in the development, in the maturation of that particular issue, and how far along the public has come in the evolution of their thinking about that particular issue, and very importantly, who you are engaging. So in the case of a large population study, for example, are you aiming your engagement to the communities from which you want to recruit participants, or are you looking at a more national or regional conversation about these issues at large? Very different communities there and different approaches that you're going to want to use.

So with that sort of as a background about the whole universe of ways to engage, let me talk about what we did and why we did it the way we did it and our experience with the genetic town halls, which we held in six cities around the United States during the summer of 2004, and over the same time frame we held 15 discussion groups online.

Now, the topic that we were specifically engaging people about was reproductive genetic technologies, and we had already done a great deal of background work around what the public thinks, knows and feels about these issues in the way of several surveys, focus groups, interviews, et cetera. So we did not use the more collaborative approach where you go into the community and ask them to help identify the issues important for them, because we already pretty much knew what the issues were and what different populations were saying, and why.

But one of the criticisms of this approach in getting feedback from the public is that you're sometimes asking people to comment about technologies or issues about which they may have little personal experience or have had little time to reflect on in depth. So a deliberative approach to obtaining information back from the population sets a stage where you provide your participants, as I said before, with more in-depth background information about the topic at hand, what the issues are. They have an opportunity to hear experts debate about the various perspectives, and then have an opportunity to deliberate with the experts and with their fellow participants about these issues.

To have a credible deliberative process really requires four things be in place. First of all, the participation must be broad and representative, and I'm speaking of that from two perspectives. First of all is your initial outreach into the community. Everybody should have the opportunity, should be aware of the engagement and should have the opportunity of participating. Within the engagement process itself, all voices should be there in the room, so that the people who are participating have an opportunity to hear what the range of perspectives are to help inform their own opinion-making.

The information that's presented should be balanced and accurate and fair, and then the environment needs to be such that there is a safe and ample opportunity for everyone to hear and to be heard. The fourth point we think is equally as important, that the policymakers, the decisionmakers are part of this process from the beginning. If you're going to ask people to take their very valuable time to think about these things and deliberate about them, they should know that there's going to be an impact from the time that they're spending.

So this is what we did. In order to ensure that the content was the same and balanced and fair in all of the locations where we held the town hall, rather than fly our expert panel around the country with us, as much as we would have loved to have done that -- it would have been a lot of fun -- we packaged them. We carried them around on a little DVD. So the town hall report that you have in the back of that is the DVD that's got those four videos.

The first one was an animated overview of what reproductive genetic testing is, and the next three we interviewed and edited together comments from experts conveying various perspectives on the three issues that were the topic of those town halls.

We partnered with a group in D.C. called the Public Forum Institute, and the recruitment for the town halls was through local coordinators who knew their communities, and they used a variety of outreach strategies, including putting notices in high traffic areas such as libraries, hospitals, clinics, grocery stores, community centers, as well as more targeted outreach to community organizations and leaders.

We also did a media push in each of the locations that we were going by placing op eds, working with local reporters, talking on local radio talk shows, placing ads in the newspapers, et cetera.

So we asked people to register ahead of time so we could monitor our

recruitment. When people came to the town halls, this is what it looked like in a couple of the sessions. They were able to sit at these round tables of about eight to ten individuals. We started the session by obtaining some background demographic information on knowledge and attitudes around these issues. So we asked 36 questions up front, eight of which we repeated at the end of the session to see if there was a shift in attitudes.

The town halls were about three and a half hours long, and they varied between presenting some of the content and then the participants taking part in small and large group discussions.

All of the participants were given these hand-held electronic devices so that we could collect the data electronically, but also periodically throughout the sessions we asked groups to call out, if you will, things that were of concern to them. I don't have a pointer, but those would get entered into the computer there and then shown up at the front of the room to help inform the large group discussion, and people could vote and then rank order on those issues.

The last half hour, then, was always a community panel of community leaders from a variety of different perspectives.

The online group, as opposed to meeting for one three-and-a-half-hour session, met for three one-hour sessions over the course of three weeks, and this was recruited through Knowledge Networks' web-enabled panel, which was representative of the general population. These are over 40,000 households that have been recruited by Knowledge Networks through random digit dialing, and if the household did not have Internet access, they were given Internet access to help get over that sort of divide there.

Because we were doing this online, for that group of people who agreed to participate in the discussion groups, we could do more data collection. So they took an 80-item survey up front, and then selected the time slot -- we had 15 different time slots they could choose from -- and mailed them all of the headsets and instructions ahead of time, and those sessions were moderated by genetic counselors. This is what it looked like on the screen to them without all of the little boxes there. But on the side was a list of the names of who was participating in their groups, and we kept the groups together over the course of three weeks. So John and Sally and Mike all got to know each other pretty well over the course of those three weeks. Then participants could request the microphone and then speak in turn.

The majority of the engagement was through audio, but on the side was a box to do text messaging, and usually we had actually two conversations going on at the same time. For those of us who have a hard time walking and chewing gum at the same time, you had the audio going on and then you had the text messaging going on.

Then about a week following the last session, 76 of those questions were repeated again to document changes in knowledge and attitude.

Another one of the advantages of doing some of this online is that you could run a control group, and we had 400 individuals matched to the participants that took the pre-test and the post-test but did not participate in the discussions in between.

So we collected a lot of data on these individuals, and I'm just going to highlight three important things. One is who participated, because it was slightly different in the two groups. We had 133 that we ended up counting as full participants in the online. So they had to have taken two of the three sessions and done the pre- and the post-test, and they were fairly representative, although a small number, of the general population.

The in-person participants differed significantly in three areas. First of all, they were more highly educated. So they were more likely to have had a college degree or higher than the participants in the online group. The religious distribution was different. The in-person participants were less likely to say that they were Protestant but more likely to say they either had no religious background or self-identified as Evangelical or fundamentalist. The third major difference is that the in-person participants were twice as likely to either have had a genetic test or someone in their family had a genetic test.

So the point is that people who take three and a half hours out of their very busy schedules to come to an engagement around this are more likely to be stakeholders and they're more likely to come with a particular background or perspective.

The second point about what we document is that we did document shifts in opinion before and after, and I'm only going to show you one data point. This is from the online group. We asked individuals whether or not they approved of the use of PGD or prenatal diagnosis for things such as fatal childhood disease, down to a more hypothetical testing for traits such as intelligence or strength, and this compares the online group with their controls. You can see that the online group started off a little more approving, but they both followed sort of that same general decreasing level of approval for the use of these technologies.

What's significant, though, is at the end of the engagement process, the control groups -- so time 1 is solid and time 2 is hatched -- the control group did not shift in their opinions over that month to six weeks. The way they thought at the beginning was the same way at the end. The participants in the discussion group, however, with the exception of the testing for fatal childhood disease, there was a significant dropoff in approval for all of the other technologies.

So the moral of the story is that engaging the public does not necessarily make them approve of what you're doing, and that's an important point.

The last point I want to make as far as some data that we collected, the topic was reproductive genetic testing, but the conversations really ranged from all areas of advances in genetics and people's optimism and concern around those issues. We kept hearing several themes come up repeatedly. One was people's concerns about the use of genetic testing, and I believe Kathy Hudson has presented before this group previously about some of our findings there. We also heard a great deal of concern about all segments of the population having access to benefits of advances in genetics.

So both of the methods did allow for nuanced, reflective conversations around these technologies. There are some advantages and disadvantages to both the online group, which by its very nature allows you to collect more data, and it's possible to track that information over time. On the other hand, the in-person town halls had a wider ripple effect because we were involving community leaders and there was media involvement. There was a wider ripple effect in that particular community.

So how does that inform having a public engagement in a large population study? Well, first of all, again, you're going to be talking to different segments of the population at different points in time, and so there's going to have to be different methodologies that are appropriate for your entire engagement strategy. The methods that we used are very exportable, and they're also expandable. Our six town halls were held independently of each other. There's no reason why -- and this actually has been done -- you can't link up the town halls and have all six of them going on at the same time, devote part of your program to a

national conversation and part of the program to local issues.

Televising town halls and having increased media involvement would also have a wider benefit in reaching a wider audience and having this broader ripple effect. I do think that tracking over time is important so you can monitor what the effect is that you're having in a particular population. That's very doable using Web resources or to use that as a tool to have supportive information for the community and participants.

We were asked specifically to address whether or not in our experience of engaging the public we felt that the public would be receptive to a large population study, and I have to say that's not a question that we asked, and that would be a reason for doing a public engagement activity, to find out that very issue.

I will say again that in general, we found that people were very optimistic about advances in genetics and the potential health benefits for those advances in genetics. Where they become concerned is where the rubber hits the road, so to speak, ensuring that everybody has equal access to those and that the information is not being used to discriminate.

Some challenges are always, of course, ensuring broad and representative representation, and that's always difficult. So engaging the community, however you want to define that, early in the process and having them part of the decisionmaking and agenda-setting is very important. The other major difference of what we were doing is we came into a community once. We were not having an ongoing and repeated conversation with that community, and that's a big difference between what we do and what some other efforts have been.

The last thing I mentioned here under barriers is the credibility issue. People look as to who is sponsoring an engagement activity because they're expecting that there is going to be a point of view and a perspective, even if it's subtle, that they're going to try to be persuaded about something. I have to say that one of the most gratifying comments that I got was after our very last town hall. A participant came up to me and she said, you know, we always hear that these things are going to be balanced and fair and everybody has an equal voice, but it's usually not the case. You get there, and even if it's subtle, there's a point of view. And she said, I have to say, I came here and there was not a perspective, and all voices really were heard. That was very gratifying to me because we had spent a great deal of effort to make that so, but it does require effort to have that sort of credible balance.

So I think with that I will stop, thank our funders who helped support this project as well as others, and turn it over to the next speaker. Thank you.

DR. WILLARD: Thank you, Joan, very much for that.

Our next speakers will be a team presentation from Yvonne Lewis and Toby Citrin. Ms. Lewis is the executive director of the Faith Access to Community Economic Development Organization in Flint, Michigan. She previously worked with Mr. Citrin on the Genetics Policy in Communities of Color project at the University of Michigan, where he is director of the Michigan Center for Genomics and Public Health and director of the Office of Community-Based Public Health at the University of Michigan School of Public Health. A lot of public health here.

The two of you will have a half hour. You can divide that any way you wish. I'll turn it over to you, and thank you both for being here.

MS. LEWIS: Good afternoon, and thank you. It is our pleasure to be here. As you can see, we're a tag team. This is work that we've done over a number of years now in

Flint and Genesee County, in partnership with the School of Public Health and our communities.

Our purpose this afternoon, as you can see in our outline here, is to talk about three engagement projects that we've actually utilized to talk about the issue of genetics and other chronic health issues. We want to share with you what we've learned from those projects.

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We also want to make some suggestions about how we might be able to apply what we've learned to this large population study. It is an interesting project, and we hope that what we share with you this afternoon will stimulate some even more interesting conversations.

MR. CITRIN: Thank you, and thanks from me also to the Secretary's Advisory Committee for this invitation.

As Ms. Lewis said, we want to do a very quick summary of three very closely related projects sequentially, which all achieved a level of participation and engagement from which we think we can learn a lot of relevance for this large-scale population study that we've all been discussing.

Next slide, please. Is there someone still pushing the button? I'm sorry, stay where you are.

The first of these projects if the one labeled "Communities of Color and Genetics Policy Project." It was funded by the National Human Genome Research Institute, and its goal was to engage communities of color, in this case African American and Latino communities, at the grassroots level to engage in dialogue about genetics issues, and to formulate recommendations for policies that would enhance benefits and minimize harms to these same populations.

The project followed a partnership model, partnership between three universities, in this case the University of Michigan, Michigan State University, and Tuskegee University, in turn partnering with 12 community-based organizations in Michigan and Alabama, each of which had constituencies and a population served, a population represented either in the African American or the Latino/Hispanic community. As your Chair suggested, Ms. Lewis played the leadership role in one of the key organizations at the community level, the (inaudible) organization, in Flint, Michigan. A couple of other people who are either going to be in the room or presenting to you were very much involved in that project. Vince Bono, who some of you know, played the role of both researcher and facilitator to a couple of the dialogue groups. Dr. Pilar Ossorio, who is on your agenda later this afternoon, was one of the valued members of our national advisory committee.

We started with a series of focus groups in order to tease out issues of concern, these following a basic educational module on genetics research, the path that it was following, and where it might likely lead. Then following those focus groups, each of the community organizations hosted and sponsored a series of five dialogue sessions, typically attended by approximately 20 members of their community, most of whom made repeat participation to dialogue sessions over the course of these five weekly dialogues. So it involved a little over 200 people, and these sessions typically ran about a couple of hours each, so the investment of time for each of these 200 people was approximately 10 hours over these five weeks.

The community organizations, and Ms. Lewis will say a few more words about their critical role, were partnering with us in all aspects of the project design and implementation, including the joint selection of facilitators and, extremely important, the selection of the place, time and mode of dialogue. So in our case, the place where the dialogue took place was the place where dialogue typically takes place, in the communities who were engaged in the project, as hosted by their community organization hosts.

The community organizations worked together with the academic team in developing the process, in implementing the process, and then, extremely importantly, in crafting the summaries and the reports and the ultimate recommendations which were used to describe what came out of the process. So the voices of the community were heard throughout the project, from beginning to end, including the ultimate end of the project where the community organizations and academic partners met with policymakers in Michigan and in Alabama, sharing the recommendations, and then had a two-day visit to Washington, where we met together with our community partners, with members of Congress, Congressional staffers, and the President's genetics advisors, again sharing the policy recommendations that came out of the project.

I'm not going to go through the recommendations. It wasn't what we were asked to do today, but just to tell you they all fell into seven topical areas: the area of access; of education; playing God/perfect children; the right to genetic privacy; genetic research, which of course was very important in terms of the presentation we're making today; genetic testing; and then perhaps the most important issue of all which cut across all the others, issues of trust and distrust.

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MS. LEWIS: As a result of one of those policy decisions, one of those important components that Toby mentioned was the education. When we were engaged in the project in those dialogue groups, some of the information that came out particularly indicated the need for additional education. We've heard that already today.

So as a result of being involved in this project, we had the opportunity to become involved with the Genetics Education Needs Evaluation project, which was funded by HRSA, and there were two communities, one in New York and, of course, we in Michigan. So we built upon the relationships that we had in the original project to develop the gene project in Michigan, but we added an element to that, because whenever you talk about community engagement, it's important to identify those groups that are particularly going to be affected by the information that's being shared.

So there were several community-based organizations that included churches, that included social organizations, Greek organizations, and adding to that was a school system. So the Lansing school system was brought into this project to look at the education needs of African Americans particularly, because that was our focus for this project.

In working on this, we continued to bring together representatives from the community to work through what those needs were. How do you determine what the educational needs are? So part of that assessment was actually having community members be provided education about genetics, basic education about genetics, and then asking them the question what do you think you need to know? What are some of those important conversations that you believe need to happen to help you be better prepared, and how might that education be facilitated? So from that collaborative process, a series of information was gained, and then we

culminated that with a town hall meeting, reporting back to the community.

The interesting thing and most important element of this was that it was not a one-time event. The same people were brought back to the table several times to work through their recommendations and suggestions. So you flesh those out, come back, and then home in on what do you think is most important. Following that small group discussion, that small group still being about 20 people or so, a formal town hall meeting was organized to help the broader community understand what the elements were of that project and how to best communicate that, particularly what we call "checking in," to see if what we said in the smaller groups was really representative of what the larger groups would say.

One of the most delightful things we found at that town hall meeting, which was attended in Flint by about 100 people or so -- the delightful thing was that the quotes and the information that we said, they responded. I wasn't at that meeting, but I can relate to those comments that were made. People were saying things like we need education because we're not sure what genetics means, we're not sure about how it will impact us. We have some concerns about how the information will be used and who will be responsible for the information once it's obtained.

So the collaborative process was very, very important. That further led us to using this same kind of concept in another statewide initiative in Flint that looked at improving cancer outcomes of African Americans in Michigan. We continued to use the process that says community is responsible enough to help determine what its needs are and how those needs can best be addressed.

So from this, working with our department of community health and a number of community leaders from across five cities within the State of Michigan, because we realized that African Americans particularly are dying 33 percent more often from cancer than any other ethnic group -- but our question remained how aware of this is our community? So we needed to raise the level of awareness, we needed to raise the level of knowledge and communication about this, to reduce the myths and, of course, in this case, engage people in screening programs.

One of the things we found out in our discussions about this is how often the issue of genetics would become a part of that conversation. The concern about total health would become a part of that conversation. So when you move from a particular issue, if you're talking about genetics, this conversation process can be used to talk about larger issues as well. So we learned quite a bit from that, and we'd like to now share with you some of the specific lessons that we learned from these three engagement projects.

MR. CITRIN: Next slide, please.

So one of the things we learned, certainly from the Communities of Color project, addresses the first question that we were asked by your staff as to whether the public would support a large-scale population study, and I think it's fair to say from the discussion on genetics research that took place in all these communities that the answer is yes, if; that there is, as Joan Scott just mentioned, an underlying faith that science has a lot of potential to alleviate human suffering, reduce disease and, in fact, reduce health disparities, and that we should allow science to progress provided that it's done in a way that is attendant to the issues that you all have been bringing up and that we're bringing up in this presentation.

We learned that if we are to achieve full engagement of the community, the community needs to be involved in all stages of the particular project or study. This means

involvement as the study is designed, involvement in developing the various instruments and materials that are going to be used in the study, involvement in the way in which the results of the study are going to be reported to the public at large and to various subsets of that public.

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MS. LEWIS: Now, as Toby mentioned, we're talking about being involved as an equal partner, not just as a passive voice or an endorsing or co-signing voice. As a result of that, in much of our discussions we understand that distrust comes from a history of a concept of them studying us, with the benefits being for them and not for us. The conversation so often happened, and we just had this a few days ago when we were talking about the issue of infant mortality, that 20 to 25 years there's been a lot of research done and we're still seeing the same kinds of results in many of our communities, even worse when you ask where is all this research and how was it translated to community, how was it utilized by community. In most cases, we have to answer the question that it was not and did not benefit the individuals who were being directly affected by it.

So there's still this huge question with this issue, which is who is going to be really responsible and are we going to be intimately involved in discussing how this will work?

The other great segue from that is all the history around race and racism in this country, particularly in the United States of America where it was a Constitutional issue as it relates to African Americans, and it still is today. Those things are not erased. They're not erased in individuals' minds, they're not erased from our day to day or institutional processes, which continue to keep that as an issue that will prevent us from being successful in delivering a good product, because the trust isn't there.

Toby said if, if we can work on being open and honest and very frank about this is a discussion that needs to happen, a very deliberate discussion, that it is purposefully intended to be a part of the conversation, because trust comes from co-ownership. It comes from really believing that you are an integral part of it, not somewhere along the line but in the initial parts of the discussion. So for me personally, I'd like to thank this committee, because we went through a little bit of a discussion trying to get here today, and you made some allowances for that. But certainly as a representative of my community, I can attest to the fact that there are opportunities for us, and we'll talk a little bit further about what that really means to the community as we think about the importance of engaging a large number of individuals across this country to address this issue.

MR. CITRIN: Next slide.

We learned something about education that most professionals in the field of education already know, and that is that education is most powerfully done if it follows engagement. If students are engaged in the subject, students will hunger for education and learning. If they aren't engaged, then all you might want to do in beaming education to them is not going to have much result. The sequence of our projects actually was from an initial recognition of relevance of the project to the community, which brought engagement in the project, and having been engaged, there was a continuing desire to learn more.

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MS. LEWIS: Next slide, please.

The other thing that we learned as a part of all of this is that the community's expectations are raised when they have been engaged, and that is clearly a difference in the amount of involvement a community might give. We still have individuals -- and this is after

five years now -- who meet us on the street and say what's the next thing happening in genetics? What are we going to do to follow up on those issues? So being involved in it from a community-based perspective keeps it relevant and in the forefront of individuals' minds.

So having raised that level of expectation, it's clear that they must understand what the expectations are. What is the purpose? How is it designed? Why is it designed? Who will benefit from it, and what will be done with the outcomes? What's the purpose? What's the ultimate goal of this involvement? Not fulfilling these expectations continues to lead to distrust and ultimately the opposition which could really sabotage the effectiveness of a project over time.

MR. CITRIN: Next slide.

MS. LEWIS: Additionally, community-based organizations which we represent are valuable, and we say intermediaries. It's that intermediate step. It's not going to be the case that you will be able to engage every individual of this 500,000 or million folks, but certainly there will be a need for some organized group within the community to maintain some synergy or some consistent engagement, consistent opportunities for dialogue. So as we developed our projects over time, they were designed so that community-based organizations would be seen in a leadership role and continue to be partners in the study.

The other unique thing that I think we've developed over time that is really beginning to evolve is the connection on a local, state and national basis of collective community-based organizations understanding these issues, particularly as it relates to research and prevention research. We're a part also of the Prevention Research Centers of Michigan, funded by the Centers for Disease Control. As a result of our involvement since 1999, there is now a National Community Committee that is representative of community-based individuals who are considered advisory board members of all of the centers as a part of that, and we've been meeting regularly for the last few years looking at how we can collectively gain some understanding about how to engage in community participatory research. It is so important to develop the capacity of individuals within our community to understand the research process, and we use a phrase in our community, "bench and trench." We believe very strongly that science has its place, and we call that the bench, but we also believe very strongly that there is expertise within communities that represents the trench where the work is actually going on, where the experiences are actually happening outside of a research framework within an institution, but bringing that into the community.

So when you work with community-based organizations at these levels, particularly national networks, when you're looking at a project like this, you have the opportunity to really expand the level of involvement and some collective thought about how this will continue to happen.

MR. CITRIN: And as a footnote to these comments about community-based organizations, we found that there was quite a differentiation in our experience of who comes to sessions, on-site sessions, when they're hosted by community organizations, as distinguished from people coming to sessions that are hosted by other organizations from outside the community. Here we did depart from aspects of, for instance, the Oregon Health Decisions movement, which found very much, as Joan Scott just reported, that it's the more highly educated people who have a particular stake in this or that genetic disease or, in the case of Oregon Health Decisions, in the health system itself who come to the dialogue.

When the community hosts the dialogue through their own organizations, you really avoid that kind of differentiation because people are simply coming to where they normally come to discuss and to formulate recommendations and to formulate advocacy.

Next slide, please.

Ms. Lewis mentioned the work that we have done together over the years on community-based participatory research. It's probably clear that the large-scale population study we're talking about isn't going to be able to be conducted exactly with all of the characteristics of the sort of gold standard of community-based participatory research, but there's a lot to learn from that research that is of relevance to a large-scale population study. The way in which knowledge is bidirectional, coming from the community to the researchers, and from the researchers to the community, can make a project much stronger, much more relevant, can make the instruments more powerful and more accurate.

The ability of people from the community that's being studied to actually have a voice in the project itself and what it leads to can help bring the participation in the first instance. Here I would suggest that there is a role that this style of research can play in education, and I guess here I part company to some extent from the sequence that my esteemed colleague, Dr. Kardia, was suggesting this morning of infrastructure first, project next. If the project, in fact, does engage the community and is fully participatory, then the project can be a vehicle for community education as it moves along, as it's being planned, as it's being implemented. One does not have to have the education first if the participation is going to be there.

Next slide.

So the ultimate summary, and it's why we chose the title we did for our joint presentation, of what we learned from these projects if really encapsulated in the word "partnership." If the project is going to be successful, it needs to be a true partnership between the researchers, those who are researched, and those having a stake in the research. We really don't like the word "consultation." Consultation sounds like a train is running over here and periodically you sort of check in and ask for advice. We love the word "partnership." We think that's what's going to lead to full participation and engagement.

Next slide.

MS. LEWIS: We indicate here that the process for partnership building must be evaluated continuously, because at times it's not so much how it's being done. At times it's more important what's being done. Unless people are feeling a strong sense of involvement, what you end up with still may not be the product that you want, still may not be utilized in a way that would be in the best interests.

So along with researching and evaluating the research itself, we suggest that continuous evaluation of the process and that partnership building be done as well. That will help lead to developing a common language, developing a common understanding, and ultimately developing the common goal and achieving that common goal to ensure the progress, identifying what the stumbling blocks are over time. When those identified stumbling blocks become clear, then there's also the possibility to develop strategies along the way so you don't get down to the end of the project and figure out, oh, we should have fixed that five months ago.

So we're continuing to find that evaluation in large-scale projects like this are a real challenge, because when you're working with people over time, particularly when they may be in a volunteer situation and just being asked to offer their time and they're not seeing the

true benefit, they're not sitting around the tables like this, hearing the ongoing dialogue, something gets lost in the translation. So there is a continuing need to work on that because community involvement is such an integral part of the process of capacity building.

If we can build the capacity -- and I may repeat this a number of times, but if we can build and maintain the ability of individuals in the community to understand this, when you get ready for the next part of it, it's not as difficult because the language is clear. I've heard a number of acronyms this morning that I never heard before, but now that I've been exposed to them I'll go back and read a little bit and I'll figure that out. But this raises my ability, then, to go into the community and say here's what's going on, here are some potential implications of this, and here are some things we need to think about.

So having the ability to do that ensures that when research is done in the community, you have a higher level of understanding, which means the project can move more swiftly and more effectively.

MR. CITRIN: Next slide, please.

Now our final comments are an attempt to apply what we've learned through these three projects to the proposed large-scale population study or resource.

It's clear, and you've already identified this, that this large-scale study proposes a major risk of generating distrust among vulnerable communities, particularly communities of color, and the reasons you have identified and we've spoken to, so I need not repeat them. But it's also clear, it seems, that the avoidance of that distrust and the achievement of participation and support is dependent on the concept of co-ownership of the concept across the communities that are most at risk from the study or that perceive the most risk from this kind of a study. If you have a sense of co-ownership and partnership, you will remove the major cause of the distrust and potential opposition.

On the positive side, if you do achieve this kind of sense of co-ownership, you have powerful advocates for what Dr. Kardia referred to as infrastructure that's necessary, what Dr. Khoury referred to as the two-pronged approach, what Dr. Collins referred to as the need to address these issues of education and policy. This can all be done together with powerful joint advocacy if one has the engagement and the partnership to start with.

Next slide.

MS. LEWIS: Another very important thing that we believe we would want to have considered in applying what we've learned is that the decisionmaking and planning needs to start now in having community engaged. Just a phrase is if you start right, you can end right. We cannot expect to have the buy-in of community if it is perceived that the train is already rolling down the tracks, there's no room for any modifications or adjustment, there's no room for voice.

If, in fact, we want to be effective at all levels, at the federal level, at the state level, at the local level -- and I recognize that sometimes individuals come in a community -- an example was given in the town hall meeting. You come into the community, you have a conversation, and that's wonderful because people do feel like I had something to say. But they're going to sit back and wait and see what happens next, and when that same thing comes around again, the question becomes is this actually the same thing? What did you do with the information we shared with you the first time? So at a local level that happens, but it needs to happen more at the state and federal level, because when policies are made, some of what happens at the local level doesn't always get filtered up. So unless those voices are there at the

time some of those final decisions are being made, things may get lost that are so integrally important to the success of that when you get back to the local level.

DR. WILLARD: Just as a time check, if you can try to finish up in the next five minutes or so, we're half an hour into this.

MR. CITRIN: Okay.

MS. LEWIS: So particularly as it relates to the health disparities, it's important that the process be explicit, the study process be explicit in addressing the issues of race and racism, and that the individual representatives of the racial and ethnic groups are an integral part and meaningfully involved in developing the plans and methods.

MR. CITRIN: Next slide, please.

This is a national project. Therefore, it's necessary to do the kind of connection with community at the national level, as well as regional and local. The number of national organizations that have local chapters and that represent these same constituencies can become partners in this project. As examples, we mentioned the National Urban League, the NAACP, the National Organization of La Raza, the AME Church, the National Medical Association, its counterpart in the Latino/Hispanic community, and on and on. These are organizations that can create the kind of buy-in for the project that are all interested in health issues, that also can translate and filter down through local chapters of these organizations into the kind of grassroots dialogue and engagement that Ms. Lewis and I have been talking about.

The National Community Committee, of which Ms. Lewis spoke, can be an extremely valuable resource because here you have community organization representatives in 20-some states, all of whom have a great sense of the worthwhileness of research and the role that community can play in research.

Next slide, please.

MS. LEWIS: And I'm sure you have this handout, so I'm going to summarize the next two slides that talk about community-based stakeholders, as well as community-based dialogues and to say that the community's signature must be there in the materials and as part of the engagement process, and of course in the dialogue process to keep the process going, to keep it open and flowing. So there needs to be a continuous opportunity for this exchange.

MR. CITRIN: Next slide, please.

You have to emphasize, along with the word "partnership," the word "dialogue." We like that word because it has to do with an exchange of perspectives and the ability to try to understand what the other perspective is. So if you can foster through these networks dialogues that involve scientists, professionals, practitioners, public health people and grassroots community people, each can get a better understanding of the other, what the project is all about, and what people's concerns and interests are.

Next slide, please.

MS. LEWIS: The next slide focuses on the role of media, and I think we all recognize how important media is to framing, shaping and maintaining the messages and pictures in individuals' minds. So it is important to have a real concentrated focus on how the media is utilized to ensure that lack of trust and fear do not become the predominant part of what people understand.

MR. CITRIN: Next slide, please.

Mention was made earlier today about a national institutional review board,

and much has been written about the kinds of studies that pose risks to groups as well as individuals, and the need of IRBs to consider those risks, those group risks, as well as individual risks, the need for informed consent materials to reflect the culture and the sensitivity and the language of the communities, and to reflect these group risks as well as individual risks, and to ensure that IRBs who do have a review role are reflective of the communities who have these risks.

Next slide, please.

The study design -- and this was spoken of earlier, so I'll just mention it -- does need to have at least a process to give some confidence that the results of the study, both the ownership of the data and how this data is going to be used, are for the benefit of the community and will not be used only for people, for instance, who have access to health care benefits, et cetera. Now, it may be difficult to give these kinds of assurances at the beginning -- next slide -- but the process of the project, the very fact that it is a partnership, that there is advocacy built into it, and that there is, as Dr. Collins mentioned, the recognition up front that the ownership of the project is in the public and will remain in the public, these can go a long way in allaying concerns that the results of the study are going to be used for somebody else's benefit and not ours.

Next slide.

MS. LEWIS: I want to summarize the next two slides, the continuous evaluation by the participants, by saying again that we cannot wait until the end. The capacity building is so very, very important to engage trust along the way for the research itself, and the importance of a shared language. The next slide talks about the fact that even the language that's being used is critical, moving from calling individual study participants subjects to actually engaging them as partners in the process; and, of course, continuing the importance of communication so that there is an open understanding of what's going on.

So in conclusion, we thank you for this extra few moments and we'd like to say that -- next slide, please -- we believe that the successful implementation of this contemplated large population study depends on whether the study is perceived as a project carried out by the public or conducted on the public. Is this truly going to be a project that is fully engaging? Partnership is absolutely the key to success.

DR. WILLARD: Thank you very much. That was wonderful. Thank you for sharing the experience you both had in Michigan with this.

The final speaker for this session, before we open it up to a panel discussion, is Mary Woolley. Mary is the president of Research!America and has served in that capacity since 1990. Research!America has been probably the strongest advocate of the biomedical research community nationally, and Mary personally has been tireless in her support not only for biomedical research but in engaging the public and in finding out what the public is thinking and bringing knowledge back to policymakers of exactly how much support the public has in general for biomedical research.

Under her leadership, Research!America's membership has more than quadrupled. It has earned the attention and respect of not only researchers but the media and community leaders in general with public opinion surveys and advocacy resource materials.

So, Mary, thank you very much for being with us today.

MS. WOOLLEY: Thank you, Dr. Willard, and thank you to everyone on the committee for this wonderful opportunity this morning and the first part of this afternoon to

learn from many of you. I have indeed learned, and I'm going to be modifying some of the things I say as I go along to put that right into practice.

So I'm going to talk to you about some but actually not all of these 10 considerations that my colleagues at Research!America and I laid out as things that occurred to us as we took a look at the plan for this study, which I've also learned now we might want to think of as a resource rather than a study.

So starting out, one that doesn't need any more explication from me because you've heard it quite eloquently from several people today is the importance of earning and maintaining the public's trust, and trust certainly does come from co-ownership in our experience, and I would say from everyone's experience in life. As I say, you've heard this eloquently from many others.

Secondly, assuring the broad support of the scientific community is important for many reasons, starting with it takes a broad scientific effort to assure that better health can be obtained for all the members of the public. It's not about one project or two, or even a thousand; it's about many, many aspects of science proceeding along in partnership, and all of them, by the way, well funded, which I'll get to at the end.

Now, I do want to spend just a moment on some big-picture context issues that, of course, have to be considered not just now at the beginning in the planning kinds of processes that you're going through, but on an ongoing basis. This has also been touched on by several of the speakers. At the moment, were this group or we in partnership with others trying to get this study, this resource, on the public agenda, we'd be competing with a lot of other things that are on the public agenda right now, and that is likely to be the case for some time into the future.

It's also true, and this has been mentioned, that there is a general distrust of the government now apparent among our population, and finding a way to position this new program in a fashion that will underscore the fact that researchers work for the public and not the other way around would go a long way toward addressing this distrust problem, at least in the part of it that we have some ability to influence. At this juncture I'll say that one of the things that we say over and over again to the research community is that we need to get better at saying and conveying to the public and its decisionmakers "I work for you," and then wait and see what the questions are that come back from whomever you're addressing, and then answer those questions rather than the ones that you think or are afraid or are guessing that the public has in mind. So "I work for you" will go a long way toward minimizing or offsetting distrust of government.

We also have a big-picture context issue right now and we have for some time in that science education and science literacy are not highly valued, or appear not to be highly valued, by many people in our society, and this needs to be addressed as well, and we all have to keep it in mind.

Then there's the issue of the overall health care costs, and most people when asked how they feel about medical or health research of any kind immediately bring health care concerns to mind. So these things are connected. One of the ways that we've seen this, and others have as well, is in a national survey conducted earlier this year where you can see where medical and health research ranks in comparison with other issues very much on the minds of the public in terms of health issues as national priorities. This does not mean that research is low, by the way. I would not say that 66 percent is a low number. But all of this happens in the

big overall context of things people have in mind, in the big overall context of health care delivery and the cost, importantly, the cost of health care.

It's also a fact right now, another piece of not so good news but it's part of the context, 60 percent now believe that the United States does not have the best health care system in the world. This is an indicator not of whether they're right or wrong about that, by the way, but of a perception that things aren't so good right now. I would say that the public is catching up to, or maybe it's even preceding expert opinion in this expression of their attitude. This is a big problem and a contextual issue, as I said.

So onto another consideration, the importance of identifying an urgent, compelling goal. The reason people get excited about something, want to participate in it, want to help plan it, want to be part of it in any way, shape or form, including paying for it and benefiting from it eventually, is that they want to be associated with something that's exciting, that they can understand immediately, even to the bumper sticker level, and get behind. Some candidate goals that certainly need addressing in this country, whether through this project or in other ways, are the importance of eliminating health disparities; childhood obesity; a very different kind of goal, but assuring the maintenance of U.S. global competitiveness, a very big issue; and then finally and always, saving lives and saving money.

I thought that Bono expressed the importance of having a big, exciting goal very well indeed. He was talking about his own work, which has been substantial, in calling for 100 percent, not 10 percent, not 30 percent or even 80 percent, 100 percent debt cancellation of the $6 billion that the poorest African countries owe the U.S. What he said was the goal has to feel like history. Incrementalism leaves the audience in a snooze. That, by the way, is why doubling the NIH budget over five years was so much more a successful strategy than let's increase it by 2 percent more than inflation for the next X number of years. People want to feel like they're part of history in order to get behind something.

I've already mentioned and it's been well covered that there are a lot of reasons to address unequal treatment or health care disparities, and the public, by the way, strongly supports that. Let's put research to work to eliminate health disparities.

I've mentioned the importance of fighting childhood obesity, important on some many levels. It's easy to say that research shows the best way to fight childhood obesity is to prevent it, but the dollars and the commitment we've made to preventing it are actually quite trivial. But getting people to understand that paying for prevention, and there's a lot of different ways to go at prevention, is a tricky communication. But if more people are involved in figuring out how to communicate it and are agreed upon the goal, we can get there.

I mentioned global leadership. The public very strongly supports having the U.S. maintain its role as a global leader in medical and health research. That leadership is by no means assured anymore. There are lots of indications that it's at risk, but it's something that's just as important to the public as it is to decisionmakers.

Saving lives and saving money. Very important, simple messages about saving lives and saving money is another way to demonstrate to the public and to decisionmakers about the value of the program you're talking about, or any other research project for that matter.

I think this point has been very well covered, particularly by my colleagues on this particular panel, the importance of the involvement of the public at every step along the way, of constantly keeping one's finger on the pulse of public attitudes and responding to real

questions that the public asks. I think Mark Twain said this better than anybody, perhaps: "Supposing is good, but finding out is better." That really is what research is about, but it's very much what interacting with the public is about as a researcher. You can do a lot of imagining or supposing about what the public thinks or will do or how they will be involved, but there's no substitute for finding out.

You're going to hear a presentation tomorrow, I believe, with some up-to-date data on concerns the public has about relevant issues. I'm going to show you just a few things from our own work.

First of all, an open-ended question, which is always useful information to get, what's on people's minds when they hear certain terms or when they hear about certain kinds of activities. It's very important to pay attention to open-ended data and information. What I'm going to show you is just touching the very tops of public perception. It's not in-depth in ways that Joan was talking about, for example, earlier, but it's worth considering nonetheless.

People say they are willing to be genetically tested, for example, but a substantial portion says no, again not in a lot of depth about this. People say they will contribute a sample of their DNA to a national databank to be used only -- emphasis on "only" -- for health-related research. People are a little more closer to split on this one. It's that how it's used issue that's been touched on by others.

Then we've also, as have others, asked some questions about personalized medicine, which has the very great attribute of having a great name. It sounds good, and I think that's what people are responding to in a positive way. They probably have very little real-life experience with what it means, and in fact a lot of us don't really know yet what it means, but we'll get there.

Now, public engagement has been stressed about what it really means. One of the things it doesn't mean, and that's the point of this slide, is public relations. By the time you're doing public relations, you're in a different area of expertise. It's important, it's necessary, but it's not the same as public engagement. Public relations comes down the road apiece, and I think always still should be driven by researchers saying and conveying "I work for you." That's the very best kind of public relations any of us can engage in.

Words matter. Words matter a lot. This has been discussed. Some of these points have, in fact, been directly addressed. One of the points I would change now, and will from now on in this presentation, is instead of saying "volunteers" instead of "subjects" in projects, we should be talking about "partners." I certainly subscribe to that, just never thought about using it as a better descriptor than "subjects," which really should be a word that's banned from the research vocabulary altogether. There's a few other things here that we're familiar with and over time have really made a difference, even as simple as talking about research projects rather than grants. "Grants" really conveys a sort of entitlement mentality that too many people associate with the science community.

Finally, the fewer words, the better. We do a lot of programming around the country to help researchers get comfortable in talking about their work in three sentences or less, three short sentences by the way. We're not talking about Faulkner here.

(Laughter.)

MS. WOOLLEY: Messengers matter. Who is talking matters. The first point to make there is that the community, the authentic messenger makes a great deal of difference. That point has been very well described already. But celebrities matter, too, and

this is important to keep in mind at the right time, at the right place. Celebrities, and in this case we're talking about Nancy Reagan talking about stem cell research, which made a huge difference to the passage of Proposition 71 in California about a year ago. She was not the only person who made a difference. You can also get into warring celebrities. The appropriate use of celebrity spokespeople is something to get help with rather than guess about. It's a job for experts' advice, but it does make a difference, and pretending otherwise is not useful.

Media matters. This has also been touched on by several speakers, and that follows on the celebrity piece, because the media pays attention to celebrities. The media pays attention to a lot of things, including controversy and conflict. It cannot be ignored. But again, some expert help makes a lot of difference. Sometimes topics just aren't ready for prime-time media. Stem cell research was one that a year ago wasn't ready. But as we all know, it's very much in the news now, and this was the cover of Parade Magazine back on July 10th. Research!America has been working with Parade for some time now, many years, and we're aware from talking to the editors and writers and others there of how important it is not to prematurely try to engage the public before they're ready. Parade Magazine is the most widely read weekly publication in this country, with 75 million readers. So when Parade Magazine is ready, the country is probably ready, and sure enough, that's what happened with the stem cell research discussion, not only because it was in Parade, of course, but from the middle of this summer onwards you've probably noticed that stem cell research has been in the media virtually every single day. That can and probably would help with a project of the magnitude that you all are considering, but it wouldn't happen right at the beginning. That's very unlikely, at least at this level of publication.

Finally I'm going to say a few words about funding. I consider funding the least significant of these considerations -- that's why it's number 10 -- because I believe that if the value has been established, and the need, and the confidence of key people in the public, the decisionmaker and the scientific community, the money will follow. It's been demonstrated over and over again that this is the case. It's not about robbing Peter to pay Paul, and it's very dangerous to get into that mindset, I believe, so that we end up talking about X number of one kind of grant compared to one big project. There is plenty of historical precedent for how money is added to the NIH budget or other agency budgets when the need is real and palpable and the public supports it.

We have a lot of public opinion poll data that gets at this point, including the sort of rubber meets the road question. When we ask people if they would pay more per week in taxes -- imagine raising taxes to pay for medical research. But actually that is, as you can see here, very well supported by the public. By the way, we've been asking this question for 12 years. This is the highest level of support for tax dollar support that we have ever seen, but it's never been below 50 percent. So it is, I think, sometimes shocking to the research community to realize that the public would be very willing to pay for more research, because fundamentally, down deep, they subscribe to the fact that without research, there is no hope; without research, we won't have better health. They have a considerable amount of confidence in the research community to deliver on that hope, and they will pay for it.

Just to underscore the point that there's a lot of money out there, this is a wealthy country, I think it's useful to think about what we spend money on in discretionary ways versus what we pay for with our federal tax dollars. These are just a couple of examples that illustrate the nature of the amount of dollars that are actually there and I think can and will

be ultimately tapped to help pay for a program of the caliber that I'm confident all of you will design and ultimately implement. When you do so, I'll be very proud to represent it to the American public and their decisionmakers. Thank you.

DR. WILLARD: Thank you very much, Mary, for those comments and for all that you and your organization does.

Thank you to all four of our panelists. We're now going to have a roundtable discussion with all of the presenters and committee members, and I'll turn it over to Kevin FitzGerald, who will referee.

DR. FITZGERALD: I didn't bring my whistle.

(Laughter.)

DR. FITZGERALD: I'd like to thank again the presenters for wonderful presentations, and perhaps we can get into what Ms. Lewis said, which is certainly going to be an interesting discussion. I don't think that will be a problem. So I'll just look around for people.

I've got Debra, and then Julio.

DR. LEONARD: So, Francis, I hate to keep proscribing what you have to do with your $300 billion.

(Laughter.)

DR. LEONARD: It's an interesting thought that Ms. Lewis raised, and Mr. Citrin, of this concept of not having them do research on us to benefit them. This is a large population cohort database that's going to be created, and researchers are going to be accessing this database through projects, not randomly but I assume funded projects that will be supported from grant funding through NHGRI or other sources. Is it possible to proscribe that the research will be funded to reflect the ethnicity of the project to be comparable to the ethnicity of the database? So that if you have 30 percent Hispanics or 40 percent Hispanics, then 30 percent of the projects that are funded to access this database have to be directed at the Hispanic population, diseases that affect that population group. I mean, is there a way to assure that it's not them doing research on us to benefit them? Because I don't know that that's been really addressed in how the database will be accessed and how the research will be done on that database.

DR. COLLINS: If I can just give a perspective from the group that thought about this. I think the idea was that anybody who had IRB approval would have access to the data. We felt there needed to be a barrier of that sort so you don't have high school students busying themselves about genotypes and phenotypes in ways that might ultimately compromise the study in terms of privacy. But the sense that the planning group had was that you want to empower anybody with a good idea to deal with what is going to be a massive amount of data.

DR. LEONARD: But sometimes money empowers people.

DR. COLLINS: Well, certainly. Lots of these people would be funded, but it would not be a requirement. But I'd like to hear the panel's reaction.

MR. CITRIN: It's an excellent question. In our work on genomics with our community partners, we've often talked about applying to all genomics research and practice the test of is this activity more likely to reduce or exacerbate health disparities down the road. One could almost consider the need for some kind of an impact statement to justify this.

I know this is very difficult when you're doing basic research to look that far down the road, but I think it's a very useful test to apply on how a database that is gathered from

all these communities is to be used, that that connection with the reduction and elimination of health disparities has got to be there if it's going to be justifiable, and this in turn can bring community engagement in the first place, and it can also bring public support.

DR. LEONARD: Because, unfortunately, it is clear that there is not an equal distribution in the research community among different ethnic populations. So you're going to get the disparities created unless there's some motivation to do the research on the non-represented groups and issues and diseases that affect all different kinds of ethnic populations.

MS. LEWIS: I think this also speaks to the importance of how the proposals or the requests are designed and that there is specific language that requires engagement of those community representatives, because as we look around, it's clear that we don't have enough African American researchers, we don't have enough in this field Native American researchers. So for us to think that we're going to put a project out there and somebody is always going to gravitate to that who is from that population is not very likely. So the language we spoke about even with addressing the issue of race and racism, that language needs to be very explicit, and there need to be some measures that ensure that that happens, which again gets to that continuous evaluation, because if it's not there, it will show up that it's not there.

DR. FITZGERALD: Julio?

DR. LICINIO: Hi. I have a few different questions. I guess I'll just throw them all out and see how the panel handles them.

I did some of the first community engagement work in genetics a few years back with the Mexican American community in L.A., and some issues that came up I think were very relevant, and I'd like to see in this much larger-scale project how these would be addressed.

One of them is this. Who speaks for a diffuse community? Let's say you have Indian tribes, which is like a defined group, and they have a self-governing body, you can go to that self-governing body which, in principle, is speaking for the community. But when you have, let's say, Hispanics in Los Angeles and you talk about community groups, who is speaking for that, with what voice, and with what level of representation?

Then how do you handle differences of opinion in the community once the community is engaged? How do you handle people who have different opinions? Maybe even if, let's say, you're including minorities because a simple majority rule might not be fair. Then within a minority group, how do you handle that 70 percent of the community thinks one way, but 30 percent thinks a different way?

One thing that came up in our discussions with the community is that there is no simple answer to this issue of inclusion versus exclusion. The threat of genetic discrimination is very real, so much so that there is this effort that Francis has made contributions to legislation barring genetic discrimination. If there was no threat, there would be no need for this legislation. So if the legislation is being thought about, discussed, and even approved by the Senate, it's because there is a problem, or a potential problem.

So if you include a minority group, they can be when the findings come out, some health findings come out that is related to a problem with that community, that they're more susceptible to this or that, they could be genetically discriminated. But on the other hand, if there was some health advantage, they would be included. If they are not studied, they would not be discriminated because the data would not be available. But then if some advance is made, it would not be applicable to them. So it's sort of a Catch-22 for the community.

My final comment or question is this. The United Nations and the World Bank have ranked quality of health care in different countries. In the United States it's consistently ranked way down, like 38 or 39, next to Cuba, and I forget which one is what. One is 38, the other one is 39. The first two are Italy and France, respectively.

So I am astonished that 34 percent of the public thinks that our health care is the best in the world. How is that possible? Is it misinformation, a delusion? How can people think that when it's so down the list?

DR. FITZGERALD: Anybody jump in, please.

MS. WOOLLEY: Can I just address that last point first, how people can think otherwise? There's evidence in so many ways that the public doesn't know what the facts of the matter are, and this is just one more case of that. But in addition, I would say that there are at least 34 percent of the American public who would like to believe that and long for the day when this country does have the best health care system in the world. I think it's important to hold on to that belief, and I would say people in every country have that. They want the best for themselves and their families, and they will support getting there if they're included on the way.

MR. CITRIN: Your earlier questions, which always pose great dilemmas, who speaks for what groups, I guess part of my answer would be that if we don't follow the model of community approval or of some kind of voting or balloting, while it's a significant question, it's not as significant if you were following that kind of approval model. Neither Ms. Lewis nor I are talking about an approval model. We're talking about a model that would engage sufficient stakeholders representative of the community so that there would be a sense that this is a project of all of us, and particularly those of us who are most at risk. Yes, if there is some kind of stakeholder group at the national level that is formed to represent this partnership, there will be people in it and people out of it, but the people out of it hopefully will have other ways to provide input on a continuing basis, and in different parts of the country, if there's a regional approach as well as a national approach, sort of following the way the study itself would be carried out presumably, there will be regions where some groups will have more of an input and others will have less.

Here again, I think the maxim that was mentioned earlier, the perfect being the enemy of the good, applies. Not everyone will be happy, but it is sufficiency of that kind of stakeholder representativeness that will give a sense that this is a project of all of us.

MS. LEWIS: I'd like to add to that that our reality is that our communities are not homogeneous. In no way are they all the same. So each time I have this opportunity, I like to make sure before the end of it that I give respect to the community which I represent, because they give me privilege to represent them and they share with me their concepts. So I share a perspective of the community, because I cannot speak fully in total for everybody.

It is a Catch-22, and I speak particularly of the African American community. We share the challenge of so many issues because we have not been directly involved in much of the clinical research. So when things come forward, they're utilized, and they don't always work the best, and we don't always know why, and then you can't follow it back and say this is what the outcomes were from that clinical trial.

So a project like this provides an opportunity for multi-level intervention and inclusion. These kinds of discussions early on help to raise these issues so that there can be some thought as to how to address them. It would be wonderful to understand, have the

opportunity to go into each community, identify it to be a part of this and understand who the people are who help make decisions for the community, because they're not your traditional people. They're not necessarily your legislators. They're like the grandmother sitting on the porch rocking in the chair. They are the church mothers who sit in the church and make the decisions even after the multiple leaders have gone. They are those individuals who run the corner stores. They are the individuals who have influence and help to make decisions on a regular basis who may never be viewed as a community leader, but they are the persons who can help us effectively engage.

But they will only do that if they have a basic understanding of what they're being asked to do and they can trust that process. That's why, as we mentioned earlier, the process is so important and cannot be dismissed as an integral part of what will happen. So I think it lends itself thinking about, as we develop this model for engaging community, those various levels that are necessary to identify who it is and how it is they will be brought in and fully engaged, and I think we mentioned earlier that engagement sometimes is a word that has different meanings to different people, like so many words.

But we're talking about people really being respected for what they have to contribute to a process of understanding. If we can think about it in those terms, I think we'll address some of the issues that are raised, maybe not fully but more intently.

DR. FITZGERALD: Joan, did you have something?

MS. SCOTT: I was just going to re-echo the fact that the public, and even communities, are not always easily identifiable as what is a community. Therefore, being open to a wide variety of approaches I think is going to be really critical.

DR. FITZGERALD: Muin?

DR. KHOURY: Well, I want to thank all of you for a very stimulating discussion this afternoon. I certainly learned a lot.

The first thing I learned and something I will incorporate immediately in my next talk is that incremental change leads to a snooze.

(Laughter.)

DR. KHOURY: Or some words along those lines.

I want to pose a question to all of you, but I'd like to preface it with a couple of statements here.

If we were able to sell the Human Genome Project 25 years ago as an initiative that's going to be far reaching, as far as biology, medicine and public health, which was only the first step -- i.e., creating the alphabet and the book of letters -- we could sell that, I think. Our leaders here in this room and others really sold that resource to the world.

I think we're now at the fork in the road in the sense that this next initiative is going to lead to the translation of that first phase of the gene sequencing and the discovery to the characterization of what genes mean for the health of populations -- i.e., the public's health.

I think as we embark on this, all the issues that were presented today, this morning and this afternoon, are going to be so important in shaping that translational research agenda, and I call this translational because it's taking it from the bench to the trench, as somebody said earlier.

Now, the question to the group here is that the appeasement of the anxiety 25 years ago around ELSI led to the funding of the ELSI program and the creation of a large scientific body of information that led to an improvement in the way we think about genetic

research, genetic identity, race, ethnicity, all kinds of things, and the answer to this question may come from what you have already presented, but I'd like you to think a little bit about this a bit more proactively.

If we were to think about the next project or the next resource or the next initiative not only as a research recruitment effort to get half a million people and follow them over time but more of a translational population-based effort to take the genes from the bench to the trench, and if you were to carve out 5 percent, 10 percent, 20 percent, whatever that number is, to do those contextual things that will allow such an initiative to move forward, how would you spend that money?

DR. FITZGERALD: Anybody want to comment? Toby?

MR. CITRIN: Well, I'll take a stab at it. In terms of spending some of the money, I think the whole process of engagement and education related to engagement is a costly project. For engaging 200 people, and this is much more intense than one would contemplate here I would think, we spent a million dollars of NHGRI's money engaging 200 people in these dialogues. This is a national project. You can't do it quite that way. But it seems to me a good share of this money ought to be spent in this process of engagement coupled with education, and a number of networks can play a role here.

Muin, you've talked about the role of the public health community and the public health agencies in the project, and presumably they would have a role in the study itself. But public health ideally is a convener of groups, and the ability of public health connected with some of these national networks of organizations that we've been talking about convening sessions that combine education and discussion could be a valuable network in order to achieve this kind of continuing engagement, and that costs money. The specifics of how it's carried out would have to be worked out.

But I think the education engagement combine the role that these community organizations play. If they're going to be partners, partners ought to be compensated the same way as researchers are compensated, and that's part of what it would take.

So these are just a few off the top of my head initial responses to your question.

DR. FITZGERALD: Joan, go ahead.

MS. SCOTT: There are some, I think, economies of scale to some pieces of it. Being creative about materials that can be used broadly is one way of getting more bang for your buck. Utilizing existing networks, as Toby said, is another way.

But starting it as early in the process as possible I think is going to be critical for overall success. So having that money right up there at the beginning has got to be part of it.

DR. FITZGERALD: Yvonne, please. Could you turn on your mike? Thank you.

MS. LEWIS: I'm struck by the way you approached this in terms of thinking about it in translation and developing the alphabet. I think if I would take it a step further, and I was trying to figure out exactly how to put this in terms of dollars and cents, and I don't have that yet except to say from the alphabet we build a glossary, and from a glossary we build a dictionary, because one of the things you said is it took talking about ELSI to get some sense of comfort with this, and if we're going to translate we need a common language. So

whatever mechanisms we have to put in place and how we have to allocate those dollars to ensure that people go from understanding their alphabet and how to make words out of that alphabet, people go from understanding that there's a DNA sequence to understanding what that means to them.

I think someone said earlier that really understanding what these concepts mean and then how that will in the future translate to us in having a dictionary that helps us go to a place and understand what all of these things mean. So from that perspective, then we think about what's it going to take to build that.

DR. FITZGERALD: Joseph? Oh, I'm sorry.

MR. CITRIN: Just a footnote. Ms. Lewis spoke in her part of the presentation to media. Media, of course, is very costly. Some of it you get on talk shows may not be. We have some masters in doing that here.

(Laughter.)

MR. CITRIN: But media not looked at as P.R., following Mary Woolley's caution, but media looked at as a way to engage the public, media as a way to actually simulate dialogue or to have a proxy dialogue in which scientists share the potential of this project with stakeholders, these are ways in which one can start stimulating national attention and hopefully national buy-in to the project, and they'll cost money.

MS. WOOLLEY: If I could just make a comment. I think one of the least costly ways to assure more public engagement faster, which I take to be a goal, whether it's for the research we're talking about here or research generally, is for the science community to start actively valuing public engagement instead of dismissing it as something that is either unworthy or too time consuming. It needn't be time consuming, and everyone can benefit from a lot more everyday engagement with the public, starting with one's own family, I might add, who are much more likely to be critical, if I can speak for my own family, than many others in our society. We can find out right there at the Thanksgiving table that maybe we're not communicating as well with non-science audiences as we might be by just trying it out on daughter Susan or son George.

DR. FITZGERALD: Thank you.

Joseph?

DR. TELFAIR: I actually want to thank the panel for clarifying a number of things, because one of the things, whenever a group gets together and has this sort of dialogue as it relates to a perspective, which is engagement, engagement at a deeper level, in partnerships and those things, a lot of terms get thrown out, and also a lot of terminology like "community" gets used without being defined. I'm glad that you clarified that community is not a physical place, it is not a group of people. It's a way of thinking about it.

I think that's important because one of the challenges is to engage people who do not readily understand or take this perspective. That's the real challenge. That really, to me, is the challenge. My colleague keeps bringing it up, and I appreciate it a lot -- that's Leonard -- the point about who are you talking to, who do we have to also get involved in the process, which is those who are in positions of making decisions on this, and it's not necessarily a lot of people, but those who already have a way of thinking about how this is supposed to work.

So I would actually both suggest that we also think of a broader way of defining the question of who should actually be involved and not limit it to just discussion of

particular groups of people in terms of race or ethnicity but looking at those who are actually at risk or vulnerable populations, like Loretta Day talks about a lot. Those are the kinds of folks, and that cuts across, to me, ethnic bounds, cuts across racial bounds, and it gets into other issues that we rarely talk about, which is issues of poverty, issues of those sorts of things, which by and large are common things that are shared across all the groups that we're talking about.

So I would say look for things that are more common, the commonalities, and be able to have a dialogue with those who make decisions such that they understand those commonalities.

The other thing is that I would suggest that, given everything that we've heard today, there needs to be some effort towards making a level of comfort for those who are in the decisionmaking process to feel comfortable with this whole idea of community engagement. I think it's one thing that I appreciate tremendously to say that scientists should begin to appreciate community engagement or public engagement or whatever, but it's another thing to bring those who are scientists and other people to that place where that is a comfort discussion. I think that's the other challenge. So I would recommend that, that we as a committee think about, and I would also be open to wondering what the panel thinks, but that's something that we who engage in community-based research and evaluation all the time are constantly struggling with.

MR. CITRIN: If I could just make a quick response, I think that was quite an important statement that you made.

When I looked at the PowerPoints for Dr. Willard, it was quite clear at least that this is not labeled, at least it wasn't in his PowerPoints, as a genetics project. "The goal of such studies, large population studies, include determining the mechanisms underlying common complex diseases," or looking at the earlier bullet, "one approach to learning more about the relationship among genes, the environment and common diseases." I think that's a powerful clause. I did not hear, frankly, Dr. Fink's labeling of the project, which sounded more like a genetics project.

It seems to me that if this project, in fact, is described as one to understand better this relationship between genes, environment and common complex diseases, then it really is a project for everyone, particularly a project for people who are experiencing those complex diseases, which again leads us to the issue of health disparities and how to resolve them. This can be a very unifying project.

Again, I kind of part company not in what Dr. Kardia said but in terms of a sequence, that the study itself can start building bridges across the social sciences and the genetic sciences by looking at all of the determinants, all the major determinants of these diseases at the same time, and it can build bridges to the community by doing the same, because our community partners -- and Ms. Lewis is one of the most valuable ones -- do understand this ecological view of public health which embraces genetics and biology in the middle bull's eye, and runs all the way out to social, family, and structural determinants in the outer rings. If the project is seen that way, it could be an extraordinarily connective project which can lead to buy-in by the community as well as by policymakers.

DR. FITZGERALD: Joan, please.

MS. SCOTT: I'd like to add one additional comment about the educational piece of it and framing it more in the context that Toby was just talking about. Particularly amongst the scientific community, there's much about the deplorable level of knowledge of

science within the public, and specifically around genetics. I don't know how my car works, but I'm a pretty good driver and I can make it work, and I'm an ethical and a good driver. So I'm really less concerned that the public understand down to the nitty-gritty of what a polymorphism is or whatever.

But the public is very capable of understanding very complex both technical issues and social issues and ethical issues and having very nuanced conversations about them, and putting them in the context of what they already know, which is the complex diseases. People can get it.

So I think education, yes, is a very important component of it, but I'm less concerned that people understand that we have 46 chromosomes in every cell than what that really means in the application of it.

DR. FITZGERALD: Yvonne, please.

MS. LEWIS: I'm also hearing that there is another community that needs to be engaged in dialogue from a different perspective. The science community needs to be engaged in understanding the language of those who are not in the science community. Toby mentioned earlier bidirectional, and we talk about bidirectional, but we also talk about cross-fertilization, which is to say that we talk amongst each other enough to begin to understand what we mean. So when you're all in a room with the people you work with all the time, and you all think alike, and you discuss a lot of wonderful things, when you walk out of the room you still all think alike. The idea is how do we get people who think differently in a room to have a conversation about a complex issue and get some understanding about how they think differently and walk out with a common way to address the issue? I think that's what's critical here, and that gets into how you translate.

So if we were to take this room as an example and have a dialogue, it would really be a conversation based upon a scientific perspective and then sharing what does that mean to me from a community perspective, and then how do we come out with language that helps us both know we understand what we're talking about. So I think that element might be a part of the process that not only are we thinking about going out into the community out there, wherever that is in the world in the United States of America, and identifying 500,000 or 1 million people and saying let's also figure out how we bring the geneticists, how we bring researchers, and how we bring community together in a discussion that helps us figure out what steps to take next.

DR. FITZGERALD: We have time for Hunt, and then one more.

Go ahead, Hunt.

DR. WILLARD: My question is going to be a little bit different in the sense that both the NIH working group and this committee have identified public engagement, and the need for public engagement is a major issue. Our job, other than just enjoying this exchange and these conversations, is to make specific recommendations to the Secretary, to guide him and his thought process for how to consider proceeding with a project such as this.

So I would ask each of you for some specifics in terms of what would be concrete specific steps that you would suggest in order to take the pulse of the public and/or to have them engaged in a project like this, because we've all identified that it's important, and you each have your own experiences in how you've done this in other specific settings. But in the context of this setting in a project of this potential magnitude, what specifically would you have us or have him do in order to bring the public into this partnership?

MS. WOOLLEY: I was just going to say that taking the pulse of public sentiment is probably the easiest thing that could be done, although saying it's easy is not the same as saying it should be quick and dirty and not thoughtful. It does need to be done well and respected once it is conducted. So I'm talking about public opinion surveying. But I think Joan has laid out very effectively the stream of getting involved with public engagement and doing it thoughtfully. There's different levels. There's simply putting your finger on the pulse, and then there's really empowering and working with members of the public.

But I think using Joan's model, if I might suggest this, using Joan's model back to the Secretary, let's say, and saying here's a model stream of how to engage the public, and we want to propose taking steps in each of these areas and move forward that way. It's going to cost money, and the further upstream you go, the more it's going to cost, but I think it's money well spent, and that's also been discussed here as to what percentage it is or how many dollars it is. I don't have the expertise to comment, but it's worth doing, and I think that's the thing to say to the Secretary, and to start now.

DR. FITZGERALD: Joan, please.

MS. SCOTT: I would suggest that the start be with clearly identifying the communities of who you are looking to engage and whose pulse you want to take, and then going to those communities to get some initial idea of the levels of concerns, just a broad brush stroke, what are the optimisms, what are the issues of concern, and then begin to focus more in on a long-term engagement process that's going to carry those communities along with you for the long haul. So as Mary said, there's this initial pulse-taking that needs to be directed clearly, but then starting from the very beginning of what's the long-term strategy to move them all along with you down the track.

DR. FITZGERALD: Toby?

MR. CITRIN: Maybe some of this has been done, but I know we talked earlier about working groups in a number of meetings and sessions involving various stakeholders, but the convening, even if it's informally, of some kind of a group that actually could engage in dialogue at the national level the way that Ms. Lewis has been talking about dialogue; in other words, that would be representative of the scientists who want to proceed on this as a scientific process, public health leadership, and stakeholders with national prominence and some credibility with communities who are very interested in health, in furthering the health of their constituencies in reducing and eliminating health disparities, and having a group like this, even if it doesn't have any official status, engaged in dialogue on how they might all come together in their constituencies to further this kind of a project and to maximize community engagement.

I think a lot could be gained from that kind of a group having a repeated series of sessions and discussions to get things started.

DR. FITZGERALD: Yvonne, please.

MS. LEWIS: I support what has been said. I'd like to add to identify representatives for the committee up front. Whatever your recommendation is, if you're recommending a committee, identify representatives from the communities of concern and have them be at the very first meeting, and allocate resources to ensure their participation, and commit for the long haul.

DR. FITZGERALD: Thank you.

We're running a little over, so I just want to ask one last quick question, just

a simple yes/no, clarification for the public since we want to empower and engage them. It is my assumption that the true partnership that you're talking about requires that everyone who comes to the table be willing to hear someone else at the table say no, I don't want to do it that way, I prefer to do it this way. Is that correct?

MS. LEWIS: Yes.

MS. WOOLLEY: Yes.

DR. FITZGERALD: Great. Thank you very much. Thank you very much for all your attention.

MS. BERRY: Thank you so much.

We will now take a 10-minute break, not 15. We'll be back here at, say -- let's just say it's going to be a little bit less than 10 minutes; at 3:20 we'll start up again.

(Recess.)

MS. BERRY: Let's get started if we can.

One thing I'll call to the attention of the members of the committee is the fact that you should have two documents pertaining to the coverage and reimbursement report recommendations, and as I mentioned earlier, one will outline some suggested editorial changes recommended by staff. If everyone would read these tonight and be prepared tomorrow to decide whether we want to go ahead with the proposed changes or whether we want to stick to the original version that we worked on at the last meeting.

I will turn it over to Hunt.

DR. WILLARD: Our final session will involve three bioethicists, and we're fortunate to have some real experts in the field to discuss a variety of perspectives on key policy issues involved with contemplating a large population study.

Could someone close the far door? That's a subtle hint to people that they should be inside and not outside.

In addition, we've asked the panelists to address or identify specific mechanisms or processes to address the issues that they raise. I don't know if you have time in your comments to address that. If not, we surely will follow up with questions specifically on that.

So our first speaker will be Henry Greely, who is the Dean and Kate Edelman Johnson Professor of Law at Stanford University. He specializes in the legal and social issues arising from advances in the biological sciences and in health law and policy.

Mr. Greely, thank you for being here.

MR. GREELY: Well, thank you. I'm happy to be here. I appreciate the invitation. Despite the PowerPoint, I am not my friend Pilar Ossorio, and in fact I'm not using PowerPoint at all. I'm not sure whether this is an eccentric affectation or laziness or a desire to actually have you watch me and not watch the PowerPoint slide. I like to think that it's because as a lawyer I very rarely have data, and if you don't have data, there's much less power to using PowerPoint.

What I'd like to do is talk about two big ethical issues in large population resources. Before doing that, I'd like to say that I think the overall issues about whether this project should go forward are quite fascinating, and I'd like to pick up on something that one of the members of the last panel said. I think having a big goal, having an audacious idea, is a really important thing. I think it has significant externalities not just in terms of public relations. It's not just Bono and people not going to sleep, but it inspires researchers, it inspires

students, it inspires people to go into the science. I think moon shots have externalities that are sometimes overlooked. I say that without having any opinion on whether this particular moon shot has a scientific value to justify its financial cost. I'm not competent to answer that and I just don't know the answer to it.

I think I am competent, though, to say that if this does go forward, it will face a host of ethical, legal, social and, perhaps most difficult and used in a broad sense, political problems, and I say that as a battle-scarred veteran of about a decade of the Human Genome Diversity Project, which met many of these same difficulties and ultimately failed to surmount them. So I do think that if one decides to go forward with this, a careful study of similar past projects, successful ones and failed ones, will be very useful in letting you know not just what methods may or may not solve some of these problems but what problems you're going to hit, because the one thing that was overwhelmingly clear to us in the HGDP was that there were far more land mines in that project than we had any idea about going into it. We discovered a few of them, to the cost of many body parts. There will be more that a project like this will hit. But looking at the land mines that have been exploded in the past or that have been diffused in the past will be very helpful if this goes forward.

Now, I was asked to talk about or to specify three particular ethical issues that I thought were especially important. The three that came to mind were, first, issues of control of the uses of these materials and data; secondly, issues of the return of information to the participants in the research; and third, issues of confidentiality. The issues of return of information to the participants in the research my colleague Pilar is going to speak about next, so I won't say anything more about that other than to say it's really important, and listen very carefully to what she has to say because I think this may be one of the most dangerous of the land mines a project like this will face. Instead I'll focus entirely on the issues of control and the issues of confidentiality, starting with control.

By control, what I'm talking about is the research participants' ability to control how the data and the personal materials, the personal biological materials that person has given to the project end up getting used. I want to start this discussion with a story about some litigation that's currently in progress in the state courts in Arizona involving members of and the Nation of the Havasupai, a federally-recognized Native American tribal government, nation, that lives in the lower Grand Canyon.

It started in 1989. Researchers from Arizona State University started a genetic research project with the Havasupai aimed, according to the allegations of the complaint, solely at a study of non-insulin dependent diabetes mellitus, an issue of great interest to many Native American groups, and certainly to the Havasupai as well. The facts that I'm going to tell you about are not yet proven facts. They're allegations in a complaint, and as a former litigator I know exactly how much suspicion one should view unproven allegations with. In this case it's a little bit modified because most of the allegations of the complaint are taken from a report written at the pay and at the request of the defendant, Arizona State, who had an independent investigation of the situation done, and that entire report is attached to the complaint.

So in 1989 the diabetes study started, bloods were taken, family histories were taken, clinical information was taken from the Havasupai, and only over a decade later did they learn that the researchers involved were not just studying diabetes among them but studying schizophrenia and also studying issues of historical origin. The Havasupai were

outraged. They were particularly outraged since they had been specifically reassured that only diabetes research was going to be done and had specifically made that a condition of their initial approval of the research.

They further were outraged when they discovered that the samples weren't just sitting at Arizona State with the researcher who had come down to Supai Village and talked to them and met them and who they knew, but the samples were distributed all over the country and all over the world to researchers they had never met, had no relationship with, and had no appropriately or misplaced sense of trust in. The result has been litigation, bad feelings, and I suspect a very long time before the Havasupai are willing to participate in genetics research again no matter how the litigation comes out.

This is a particularly powerful example, I think, of the fact that people's interests in the research that is done with their material and their data are not limited to things that affect their physical health, their personal economic well-being, their insurance status, but people sometimes care about what you do with their data because they don't want to be complicit in certain sorts of research. The Havasupai did not want to be studied for schizophrenia. They felt that it was going to be a stigmatizing study no matter how it came out, and it wasn't an issue they wanted examined. Similarly, they did not give permission to and did not want to be part of a study of the history of their population because they believe they know where their population came from and had no interest in abetting other theories, including that sometimes referred to as the "BS hypothesis," the Bering Straits hypothesis about where their population came from.

Personally, I would be outraged if I discovered that material I had given for one research project was used, let's say, by English researchers to study the intelligence and genetics of the Irish, since I have a fairly good idea how that might come out in the hands of English researchers. But more generally, any sort of research into race and intelligence using material that I had given I would feel is a betrayal and had made me complicit in research that I did not want to take part in. Now, those are my sensitivities. Other people will have other sensitivities. They may not want their data or information about their family members to be used in research in mental illness, research in sexual orientation and genetics, research on alcoholism or addictive personalities, or a variety of other things.

But people will feel betrayed if their research is used for purposes that they think are bad purposes without their knowledge or consent.

Similarly, although I think this is a lesser issue but not a trivial one, people often, at least traditionally, take part in research in part because they trust the researchers who come to them. They trust that Dr. Collins is really going to look after their interests and be interested in cystic fibrosis. They've met him, they've shaken his hand, they've looked him in the eye, they trust him. I think very few subjects, very few research participants or research partners have any idea, regardless of what the informed consent form says, of how broadly their samples and data might get distributed by people whose eyes they haven't looked into and for whom they do not have that level of trust.

Now, in the context of large resources, the creation of libraries, resources like this would be, what I once tried unsuccessfully to get termed genotype/phenotype resources, this produces a real dilemma because you can't successfully ask people about each and every research project that happens throughout the history of the databank or throughout the history of the resource and give them full informed consent, get their full informed consent

about each and every use. It seems highly impractical because there will be hundreds of uses, if not thousands, spread over time. And even if you were able to have the budget to go back and individually reconsent people on each one of those, I think you'd quickly find that people were sick and tired of seeing you and didn't want to be reconsented after a while on each additional molecule involved in pancreatic cancer or involved in asthma.

On the other hand, I do think that there's something phony about the idea of informed consent for these kinds of resources. The idea of informed consent, both in general and as laid out in the common rule, is consent in which the research participants -- I'm trying to avoid the word "subjects," which I agree is a bad word -- the research participants are informed about the specific risks and benefits of the particular research that's going to be done with them or with their data. How can you do that with a resource like this? No one has any idea what specific research will be done, what particular diseases or genes or environmental effects will be examined. The whole idea of the resource is to make it available for people to do everything that seems important and useful over time.

So even calling it informed consent I think is a misnomer. I'm not going to take the position that as a result none of this should be allowed by IRBs under the common rule, but it is a real problem with the issues of consent around participation in resources like this. The consent is not truly informed, cannot be truly informed, and yet on the other hand, for practical reasons, when we know enough about the specific projects, it really doesn't make sense for us to be able to go back and reconsent everybody on every specific detail. It's a dilemma.

Possible solutions? Well, the first thing to say about any possible solutions is they're certainly not perfect. This is a real dilemma, a real problem, and there are no perfect solutions to it. But there are ways, I think, where some of these can be mitigated, involving two steps. First, at the beginning of the process, try to find out if there are specific issues that the research participant does not want his material or her data used for. You could do that in an open-ended affirmative way: "Is there any research you don't want done with your material?" I think that's unlikely to be very successful or very realistic.

One might also imagine an opt-in, give somebody a 12-page list of different research topics and ask them to check all the ones they're interested in. That doesn't seem very meaningful to me either.

A shorter, more targeted opt-out might actually be meaningful, listing things that you have some reason to believe might be sensitive, might be issues that some of your research participants might not want their materials used for, and ask them to check yes or no in advance.

Even that I think is only a moderate step in the direction of protecting these interests of people who may not even know what interests -- know that they've got interests in these issues until something comes up.

Another alternative and one that a Veterans Department project that I've been involved in has endorsed is to have continual monitoring of the subjects of the research topics that are involved either, or I think better, both by an IRB and by a group drawn from the research participants themselves, and have them discuss the new protocols that are proposed and see if they think there's anything here that's particularly sensitive. If they think there is something that a significant number -- weasel word; what percentage is a significant number; how do they know if it's a significant number. But if there's something they think a significant number of the research participants might object to, then they'd have the power to require

individual reconsent.

Now that I strongly suspect would happen in a very, very small number of these projects. I suspect that no one in the country is going to be particularly personally involved or emotionally attached to issues of pancreatitis, or issues of asthma, the pharmacogenomics of different asthma drugs. But when we get into behavioral genetics issues, I think then the likelihood is much greater, and the alternative to doing something like this is to have a situation where you've got a research participant who, years after signing up for this good, noble thing, discovers that his DNA or his family history or his health records were used for something that he finds abhorrent, in which case I put it to you that he feels cheated, betrayed, unhappy, and he has some grounds to do that, some appropriate grounds for that.

Now, if you take my position that some sort of control mechanism is appropriate, it does rule out one alternative. It rules out the alternative Dr. Collins mentioned a moment ago. I'm not sure this was his full plan, to make the material open to anybody who has IRB approval, or putting it even more broadly on the Web. You would need some sort of check, at least a listing to make sure that data and DNA, data and materials from people who had said they didn't want to be involved in this particular research topic wasn't involved in that topic, and I think you should also, for sensitive issues, put it before a participants board, as well as an IRB. So it rules out one alternative.

If that alternative is really important, if that's what you need to do to make this successful or to make it as successful as you hope that it will be, so be it. But make sure that the informed consent for it warns people up front that you have no control over what your data and your materials are used for. They may be used for things that you disagree with, and if that happens and you find out about it, don't complain to us. Put that in English, not in informed consent-ese, and don't hide it at the back of a 20-page consent form.

Second issue, confidentiality. This is another issue where there is an enormous problem. Americans are enamored of privacy, enamored especially of health privacy, and it's confronting an issue of which this is just one small part, an economic and technical reality that is, in the words of one Silicon Valley mogul, "Privacy is dead. Get over it." The push which I think is inevitable for more computerization of data, inevitable I think because of all the advantages that come from that computerization and networking and access of data, invariably undercuts the possibility of promising people complete or even very full confidentiality.

Now, in terms of confidentiality, most research goes forward in sort of a key system where the specific researchers may not know the identity, somebody somewhere knows the identity but it's hidden behind a code. There is a key holder someplace that has, of course, possibilities of abuse if the key holder somehow cheats and decides to use this information for bad purposes. Personally, I think the odds of that are extraordinarily low and can be made lower with appropriate sanctions, but they cannot be taken to zero. People who take part in this research cannot be promised confidentiality. They can be promised the best confidentiality we can offer them.

Despite what I've heard occasionally from the computer folks, it doesn't look like there's a technical fix for this. I've heard a lot about one-way encryption or hashing encryption followed by a lot of movement of hands as it comes to be explained, and as far as I can tell from cross-examining computer scientists in some of my classes, it's not going to be a useful technique particularly for a project like this where additional data will be added

longitudinally. One-way encryption works all right if you're only putting data in once and there's no way to ever decrypt who that is. But if you've got data from me and you've put it into the database, and later you want to add more data from me, there's got to be a key somewhere. Somebody, somehow, has to know that file 17648G is Hank Greely. Once you've got that, this one-way encryption idea no longer will provide the technical fix that people hope for.

But there's a more fundamental confidentiality problem. Useful data sets are rich data sets. Rich data sets are identifying data sets. Professor Latanya Sweeney has published some nice work on this. I was born on June 25, 1952 in Columbus, Ohio. I actually should go back to Franklin County and look sometime, but my guess is, given the demographics of the era, there were probably seven kids born that day, of whom I'm guessing there were four males, three white, one black, three females. If you know that information about me, that I was born then and there, and you know my sex and my race, you're down to three people in the world. If you're really interested, you can find out which one of them is me. I happen to know that one of them is my cousin Mike. We were born on the same day, the first grandchildren of our grandparents. He will never let me forget that I'm 20 hours older. He's 5'6", 130 pounds. It wouldn't take much more data to distinguish which one of us was me and which one of us was him.

If you're born in a small town, the identifiability becomes even easier. If you're a famous person, your identifiability becomes even easier. If you live at the zip code for the White House, it's not going to be all that hard to identify you with just a little bit of data.

Now, as the world becomes more and more wired, this becomes a bigger problem, because more of this data is put online. Interestingly, I think the thing you've got to worry about for a lot of this place and birth date data is the genealogists, who are busy as beavers online, putting all sorts of databases online. Genealogy is apparently second only to sex or pornography in terms of its interest level on the Web, and genealogists are constantly putting new data sets online. So right now you'd have to go to the Franklin County records to look up my birthday, but that's probably not going to be true for very much longer, and once that becomes possible, the ability to identify people with deidentified data sets becomes much stronger.

Now, you can fuzz the data sets. You can say not born on June 25, 1952 but born in 1952. You can say not born in Columbus, Ohio but born in the Midwest. Every time you do that, you lose something of potential scientific value. The real harm there, the real problem is you don't know how much value you're necessarily losing. There are seasonal variations in disease incidence based on what season somebody is born in. There are some things like schizophrenia which have a higher or lower rate depending on what season you're born in. There are regional variations and issues. I went to my ophthalmologist, who looked at my retinas, a normal exam, and said were you born in the Ohio River Valley? I said, well, close. He said, well, you've got histoplasmosis scarring on your retina, which is very common in people from the Ohio River Valley.

Now, you can try fuzzing the data. As you fuzz the data, you lose some medical and scientific value, and you don't know how much you lose.

So the dilemma here is, the more useful you make the data, either in terms of the completeness of the data set or the wide breadth of people who are able to get it, the less you can promise people confidentiality in it, and even anonymity. Even if you try to make it completely anonymous, there is no key anywhere. You can't successfully do it.

Is there a solution? Not much of one. The only solution that I can recommend is complete and total honesty, but that will be expensive. People are leery enough about their privacy that if you tell them we can't promise you confidentiality, and even if it's anonymous, somebody who cared enough might be able to look at all this data and figure out who you are; we don't think anybody is likely to do that, we think the odds are low, but in good conscience we have to mention to you that that's a possibility, you will lose some research subjects I predict, and probably not a trivial number of them.

The alternative, though, is to not tell them that, let them sign up based on their understanding that there's broad confidentiality protections, and then feel betrayed when they discover that their identity has somehow been blown and that their confidentiality is not there. As I say, I think this is a much bigger problem than just a problem for large population research resources. It's a problem all of American health care has to deal with that stems from a mismatch between our public expectations of privacy and the realities of the society we live in with respect to privacy.

Well, there are a number of other important issues, but I suspect I've already gone over my time. Let me just close, though, by saying I think this is really important. I think it's really important to line up the ethics of projects like this so that people do not feel betrayed, do not feel that they've been lied to or mistreated, and I think it's important for two reasons. One is because it's the right thing to do. If you've got subjects who feel that you have mistreated them, lied to them, deceived them, betrayed them, then at the very least you've probably done something wrong. You may not have been evil, but at the very least you didn't communicate as well as you could have, and that's an unethical result.

Secondly and more pragmatically, it's bad for science. Any research subject who feels betrayed and mistreated is not a research subject who is likely to sign up for more research. The Havasupai aren't likely to do a lot more research anytime soon. They're also not research subjects who are likely in their role as citizens to lobby for, vote for or support biomedical research. Treating research subjects well is ethically important for science and for scientists. Treating research subjects well is politically and pragmatically important for science and scientists as well.

Thank you.

DR. WILLARD: Thank you very much, Mr. Greely. I appreciate that, and we'll hear from you again once the full panel has spoken.

Our next speaker is Dr. Pilar Ossorio. She's an assistant professor of law and medical ethics at the University of Wisconsin Law School and is also an associate director in the Center for the Study of Race and Ethnicity in Medicine at the University of Wisconsin Law School.

Thank you very much for being with us.

DR. OSSORIO: Thank you, and I do have some slides, so it's okay, I'll just say next slide, and we can go to the next two. There we go.

I'm going to talk about reporting results back to participants, and I should say that Professor Greely and I are both involved in a project at Stanford University in their Center for Excellence in Ethics, where we have a working group that has been discussing this particular set of issues very intensively. We will be coming out with a white paper soon, and I suspect that you will all eventually get that white paper. Some of the things I'm going to say today I will actually highlight as the results of those discussions and where we've come

seemingly to a consensus, and others are my personal analysis and I'll try to highlight that.

So I wanted to start just by highlighting some sort of background conditions and assumptions, things that I understand about the proposed project here, importantly that it's going to measure a lot of environmental exposures. It's not just going to be about gene sequencing but it's going to measure environmental exposures. Probably ultimately some people will have a lot of gene expression work, proteomics, epigenetics done, so there will be, at least for some participants at some point, almost something like total cellular characterization that will be associated with lots and lots of not just medical data but other data. So you will have people who have biological material in a repository along with more data than most people would ever have in their medical record.

This means that inevitably you will find out medically, clinically important things about people as you go through this project.

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I also want to think about this, somewhat separating the issues in terms of building the resource, that is collecting specimens and data initially, and then follow-on studies. That would be studies done by people who are using the resource. The reason to do that is because I think there might be, in general, some differences in those two categories, differences that are ethically important and that have a pragmatic sort of impact on what you might do. Those differences involve the proximity of researchers to participants both in space and time. So people doing follow-on studies, people might develop clinically relevant information, but they might be crunching data five years after the data and material were collected.

The fact that it's five years later that you found something clinically relevant and that you may not have any interpersonal relationship, the follow-on researcher may never have met any of these participants, was not the person who collected biological specimens from any of them, that may influence the ethical obligations or the permissibility even of reporting back any of this information.

Follow-on studies may be more likely to generate information that's not yet validated, and they may also be subject to the regulatory regimes in slightly different ways, which would affect how difficult it is to go back and report information. So I think we need to realize that there's a lot of complexity here, because there's a whole set of issues around reporting back information when you're first building the resource, and there's a somewhat separate set of issues about reporting back information from people who are doing follow-on studies.

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So the first thing I want to say is Francis mentioned earlier this morning that there are lots of people who have thought about this issue, there are lots of papers, a number of different policy reports, including one that the Secretary's Advisory Committee on Genetic Testing, I think, put out, a number of policy committees that have studied this and made recommendations. There's not much consensus, actually, and I think that some of the issues that this proposed project raises are issues that really haven't been addressed fully, or not addressed at all by the proposals that are out there.

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So there's the obvious spectrum of practices and proposals. At one end of that spectrum is not returning any individualized results, and I should say that right now I'm very much focusing on the return of individualized results to individual participants, as opposed

to aggregate results to a community of people, or even aggregate results returned to participants individually. I'm assuming that there will be some felt obligation to return, to make publicly known and available the aggregate results of research done with such a project. So that's one of my background assumptions.

So we're really talking about individual results, and in fact the practice of most genetic studies up until now has been not to return individual results, and that's partially because a lot of these studies we weren't yet collecting any information that had been validated that was viewed as clinically useful, and the practice of not returning results was initiated in that context. But now things have changed, and so people's views about the permissibility of not returning individual results I think is beginning to change, and in this project, as I mentioned before, you aren't just going to have genetic information. You may have lots of other clinically relevant information where the clinical utility of it might be very well known.

But at that end of the spectrum, don't return results, that's where most genetic studies have been. That's where a lot of IRBs have been. So a lot of IRBs are very reluctant to approve protocols where individual genetic results are going to be returned.

Of course, beyond that end of the spectrum you have everything from sort of a very limited set of clinically relevant results might be returned to almost any clinically relevant information. One big battle that we're having in the working group is where does reproductive information fit in, or with respect to genetics where does carrier information fit in. It may be very important to people. In their lives, their reproductive choices may be as important as their personal life or death medical decisions, but a lot of the ethics guidelines that are out there, to the extent that they discuss returning results, either don't treat reproductive information as the kind of results that are very important or that must be returned, or they just don't talk about them separately at all.

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So I thought I would just take one moment to say that there are good reasons not to return individual results. First of all, I think if there's any unanimity with respect to genetics, in particular it's that you ought not to be returning results unless they're clinically validated; that is, unless, first of all, they have been analytically validated, but also that we know something about the relationship of having a particular allele to a particular medical outcome.

There's good reason. The balance of harm and benefit is likely to tilt towards not returning results when you don't really know the meaning of those results. The costs of sharing results when they're ambiguous, when you don't know their implications, are going to be higher. A lot more education will have to go into that, a lot more difficulty in interpreting the results, and so forth. So I think there are good reasons for not returning clinically validated results.

Also by not returning results you're increasing opportunities to maintain confidentiality and privacy protections. To the extent that you return results, you have to have linking information back to individuals, and you have potentially a number of people getting in contact with them from research projects.

Again, this issue of sort of the relationship between the researcher and the participant. In cases where there's no direct personal contact of any sort, the value of reciprocity, of some kind of mutual obligation, mutual sharing, tends not to be weighed as strongly certainly by researchers, but I would suspect by participants as well. Secondly, the

information may be already outdated in some way. The person may have already discovered it. If you don't find it out until five years after they gave material and information, they may already have found this out, for instance. So some people would say that if it's distant in time and space, that there is less of an incentive ethically or otherwise to provide the information.

I think the final thing, and this is important, is that not returning back results helps to maintain the kind of cognitive and legal distinction between research and the provision of medical care. What we've been talking about this morning I think in some ways, for some of the researchers, is going to very much blur that line between the provision of clinical care and the doing of research, and sometimes it creates conflicting obligations that are very, very hard to reconcile for the researcher him or herself, and a lot of confusion for the participant about what it is that they are going to get out of this project.

I think there are lots of ethically permissible possibilities in there, but we need to get really clear, you need to get really clear, about where you see the lines drawn in terms of what the project would provide to people and what it wouldn't, and then be able to very clearly communicate those boundaries, because we already know that participants in research have a lot of confusion about the distinction between research and medicine.

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So going on to say that it's pretty clear that a project of this sort will almost certainly have to return at least some results. Then you get into the really interesting questions, which are which results, to whom, how, what is the process of returning them, and when would you do it?

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I would reiterate that there's a pretty wide agreement among researchers, among ethicists, among all the policy recommendations, that results shouldn't be returned unless there is some analytic and clinical validity. For sure, analytic validity. I think legally there would have to be -- at some point in returning results it has to go through a CLIA-approved lab, although I am very aware that many researchers believe that their lab does a much better job than the CLIA-approved lab to which they sometimes send their specimens. But nonetheless, legally that would have to come in there somewhere.

But clinical validity as well. Again, I would say there's fairly broad agreement that we don't return results when we don't really know what they mean.

There are lots of reasons in favor, and I tend to think about this set of issues as there's going to be a very, very small domain of research results, if any domain of research results, where it is obligatory to return those results. There will be a much wider domain where it will be permissible to return those results. We have reasons in favor, perhaps reasons against, both ethical and pragmatic. So it's going to be a weighing and balancing. But if you look at all the recommendations and the kinds of things we were coming to agreement on in this working group at Stanford, it would be when the results have very serious medical implications for the participant directly, when there's an urgency about knowing these results, when the results would change the medical management in some way. So there is a certain debate. What if you find something very serious but there is nothing that can be done about it? Are those the kinds of results that ought to be reported back?

I think there are reasons in favor, but there are more reasons in favor of reporting back results where it's both serious and you could do something about it. Where there's a more robust relationship, like a face to face relationship between the participant and the

researcher, and the value of reciprocity is greater, their expectations of what you will do on their behalf is greater, and it won't come as a surprise if some complete stranger drops in on them and says, oh, by the way, I found this out about you and it's really important for your medical care; and then as a matter of respect for participants. I put that in because there's not a lot of research on what participants want in terms of getting results back, but there are some surveys and a few interviews, and mostly they show that participants have a fairly high degree of interest in getting results back, and also in the few instances where at least genetic results are being given back, mostly we haven't seen real harms coming from that, although anecdotally there are certainly anecdotes and individual instances, not so much from genetics but from other areas of medicine and other areas of clinical research, where people have gotten back clinically relevant results and found it to be very burdensome and maybe something that they wished they hadn't learned.

So participants are going to have a range of views about what results they might want back and a range of experiences if they do get results back, and there's not a lot of data out there on this right now. But I do think that the data we have suggests that many participants would like at least some results back.

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So going on, which results would we give back? There are a number of interesting questions that are raised. One of them is whether the nature of the research gives ethical or other kinds of reasons for returning back results. For instance, does it matter whether you're doing a study to look for a particular gene/environment interaction, like you're doing a study looking at prostate cancer, and you find something clinically relevant about prostate cancer that a person probably doesn't know? Or what if you're doing a study about prostate cancer and you find genetic information suggesting that the person is likely to have long QT syndrome or has an oncogenic BRCA1 mutation?

When you're doing these big studies, there will be people who have a significant portion of their genome sequenced, and you will find something in their genome that is clinically relevant, and it may not be anything that was the particular subject of the study initially. So if you're going to report back results, does it matter whether it was an incidental finding in the context of these very, very large studies? What does incidental even mean if you're doing non-hypothesis-driven research?

In the working group, my belief is based on recent phone calls that we've had that there is at least a category of research for which it wouldn't matter, or a category of results that are seemingly so important for a person clinically that it wouldn't matter whether they were incidental findings or findings that were sort of as the direct focus of your research that they might need to be reported back. Does it matter that in these very large studies it's foreseeable that you will find something, or if this is something that nobody ever foresaw? Those might be different categories to which you would attach different degrees of permissibility or obligation to report.

Also, another question that, at least in our working group, we debated a lot is do researchers ever have a duty to look around for clinically relevant information? So if we've got sequenced data that was just churned out by a machine, does somebody have an obligation to go look and see what your BRCA1 allele or other clinically relevant alleles, what you have? There wasn't agreement about that. The way we currently do research, it wouldn't be hard to put a query into the computer to look for all of these things, but different individuals

you're going to find different clinically relevant things, and we couldn't come to agreement about whether or not there was a duty to actually go searching for clinically relevant information.

My own personal feeling about this is that there's not and we ought not to set that on researchers.

Also, is there a right not to know? Almost all of the ethics guidelines would say that there is a right not to know, but interestingly, many clinical researchers say no, and I can tell you that in front of our IRB we get people who say I would not have someone in my study if they said don't give me back clinically relevant information. I think the dividing line here is really people who are clinicians and who, in the course of their research, have contact with participants or are doing a clinical exam. Their feeling is if I find something incidental or something I was looking for that's clinically relevant, it's my obligation to tell this person, and partly that's because they're in a context where their duties as a physician and their duties as a researcher are both coming to the fore, whereas many of the people who are doing sequencing or other kinds of cellular analyses are not physicians, they're not having direct personal contact, and they're feeling that I see something in these data but I don't really relate them to a person, I don't have any connection to that person, diminishes their belief that they ought to report back clinically relevant results no matter what.

Whether that relationship should make this much of a difference is a matter of debate. Some people think it should not. I think as a practical matter, it does.

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So our working group is going to end up proposing three categories of results that would have different degrees of obligation or permissibility with respect to reporting back, and that's not so different from a couple of previously published papers. Other groups have come up with some similar kinds of recommendations.

So category 1 would be results, whether they're genetic or other kinds of results, that you would be obliged to report back. It wouldn't matter what the focus of the research was, and it wouldn't matter who was doing the research, whether they were doing follow-on research or what, that these results would be perceived as so important that you would report them back. There was really, as I said, no agreement on whether there's an obligation to actually go searching for that kind of information, but I think many people felt there was not.

Category 2, which would be a very broad category, would be things that it might be permissible to report back, but it's discretionary. One thing about this category is that to the extent that you're going to do it, we felt and many other groups have felt that you have to plan for it up front, have it in the protocol, have the IRB see it, have it in the consent form, again to delineate very clearly what they might get back, what kinds of future contacts they might have from researchers if they choose to participate, and so forth.

There is a category 3, which would be information that is not permissible to report back.

Category 1 might only include really very, very few things.

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So we had the three categories, and that addresses the question of what kind of information should you report back, and in category 1 are things that are so important to someone's health and their health care decisionmaking now that you would report them back.

Everything else is either discretionary or impermissible to report. Then the question is how, and the method would depend somewhat on the category. So we felt for all categories, if it's going to be reported back, it has to be approved by an IRB, included in consent, and it has to be reported back by a person with relevant expertise, and in a project like this that could be quite complicated because different people will have different alleles that might be medically relevant. It won't just be one person or two or three or four people who are associated with the project who would have that expertise, and that's just the genetics. What if you have some other finding?

Think about it. What if you find that some group of people is having a very toxic exposure to some chemical in their neighborhood or in their work environment? You might find that in such a project where you're collecting a lot of environmental information. How would you report that back, and to whom, and would it just be to the participants? There are going to be a lot of issues there, and you need people with relevant expertise to do it, and figuring out who those people are when a lot of different kinds of expertise may be relevant is going to be difficult. We didn't go so far as to figure out the nitty-gritty details of this, but one of the things it suggests is that the more you want to report back, the more expensive it's going to be, the more personnel you would need dedicated to this process in some way or another, maybe not full time.

Of course, for genetics, it has to at some point be validated in a CLIA-approved lab. We didn't exactly agree on when and with what specimens. So we actually came to agreement that there are a range of possibilities of when in the process of reporting back it would go to a CLIA-approved lab.

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There's also the question of how. What kinds of contacts? We figured for category 1, the initial contact might be by phone or by letter. However it happened, it ought to invite people to contact you and have a discussion about a clinically relevant finding, and it ought to be formulated in such a way that they knew that there was something serious, and that it had to be followed up. So if you make some initial contact and people don't call or write in or make any attempt to really follow up and find out about the clinically relevant information, that there is a fairly strong obligation on the researchers to follow up, try second contact, make sure they really got the letter or received the phone call, and it was a person and not just a phone machine.

Every effort must be made to have face to face delivery of information when the actual discussion of the clinically relevant information takes place, and there's no obligation to provide follow-up medical services, but at a minimum you should be able to provide referral information.

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DR. WILLARD: Will you, perhaps in the next few minutes, wrap up please?

DR. OSSORIO: Sure.

I guess I would go just on category 2, we thought that there might be the need for something like a DSMB or a similar kind of committee to help researchers decide, in that permissible category, when at least some results were actually at the level of significance that they ought to be reported back.

DR. LEONARD: What is a DSMB?

DR. OSSORIO: A data safety monitoring board.

DR. LEONARD: Thank you.

DR. OSSORIO: Next slide, please.

There are also questions about when. Again, this comes back to what happens if you have data sitting around somewhere and then years later somebody finds out, oh, there's some real medical significance attached to a particular allele? Do you have to go back and continue to review the data that you have to see how new information affects the significance of the existing data? There are lots of questions about that that we didn't come to agreement on, but I'm just going to highlight them now to say they're actually important questions and you need to come to some agreement on them.

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I'm going to skip that one and go to the very last slide, I think. Actually, this is not the last slide. There was agreement that you ought to give participants options, and the options ought to include reporting back to the participant and/or reporting back to the doctor or primary care provider or somebody like that. They also ought to have the option of not getting information back. Although some clinicians didn't like that, at least our working group thought, and most ethicists believe, that there is something like a right not to know.

With respect to families, there was pretty strong agreement that there is no obligation to give this information to families, but that it ought to be spelled out for participants that this information is important to their family members, and that ought to be part of the discussion and the follow-up.

Next slide, please, which I believe now is the last. Yes. So I just wanted to sum up, then, in my last slide that a lot of this is about what will be permissible rather than what will be obligatory. So you're going to have tradeoffs, because reporting back is going to add a lot of cost. The more you report back, the more cost it's going to add. So there are tradeoffs between your desire to report back and to create benefit for people by doing that, and the amount of data you can collect, the number of participants you can have in a study, et cetera.

Also, the issues of reporting back intersect with the issues about who you include. So on the one hand if you include people who are not insured or have very little access to medical care, does it ever provide a benefit? There's debate about that. For instance, you might end up creating more constituencies who are pushing for more things to be covered by Medicaid or Medicare, for instance. On the other hand you might report back something of real clinical relevance to somebody when they couldn't do anything about it, and they would view that as much more of a harm than a benefit.

Finally, I would say also this is where your consultations and interactions with communities, your community engagements, could help formulate the project with respect to within those bounds of permissible reporting back, what kind of information might people most want, and under what conditions and things like that. It actually gives a lot of opportunity for ethics experimentation, as well as scientific experimentation.

And I will stop.

DR. WILLARD: Thank you, Dr. Ossorio.

Our final speaker for the day is Troy Duster. Dr. Duster is Professor of Sociology at NYU and also holds a position of Chancellor's Professor at the University of California at Berkeley.

Dr. Duster, welcome. Thank you for being here.

DR. DUSTER: Well, first of all, some truth in advertising. I do have drinks with bioethicists, and I've been on committees with them, but I'm not a bioethicist. I'm a sociologist, and that will become clear in my remarks. I sat with three years on the ELSI working group, and just to give you an example of the kinds of issues which occur and recur, I would say that over those three years the most contentious topic that we dealt with was access to storing tissue samples. We had disagreements about many issues, but we often came to some kind of grudging consensus. On access to stored samples, we had no capacity to come to consensus.

Now, sociologically, I put that other hat on right away. What I was seeing was that interest groups, people in the biological or molecular fields or pharmaceuticals, anthropologists, had different angles of vision on this topic about access to stored samples. Of course, the bioethicists took what would be called the extreme position, no access unless there's consent before. The people in the research community thought this was kind of crazy because we're talking about delivering health to people. So how could you be against looking at a data set when if you really examined it with some care you could actually bring health to people? That's by way of prologue.

The prologue is that I'm a sociologist by training. I'm not a bioethicist. What I'm going to do is to step back from the project and make some rather broad statements, and then become more specific in the short time I have. I can collapse this presentation or expand it based upon the time allotted. I think I'll collapse it.

I thought it useful to think about this kind of project using a metaphor of the Chinese game of go. At the very beginning of the game, an infinite number of possible moves. But when you make the first two or three moves in the game, it limits almost dramatically what's possible. The same is true for a large research project. When you first start off, you've got a whole field of possible categories of inquiry, but when you begin to use in that first cut what the categories are, like in the game of go, you limit what's possible from thereon.

Now, let me start with a question that was asked of me, what might be one of the major concerns. Let's take the topic of does the research represent the population. Depending upon how a society is organized, the very categories of who is represented is vital to stage 1 of the study. Let's take a case where you have a society that's divided into Hindus, Moslems and Christians. Those are the major dividing lines between the categories of people in terms of access to resources, who has power, and so on.

Well, in that situation you would say we have to use that as the taxonomic system when we're talking about representation. Well, let's be specific. Let's go to India. Hindus have the most power there. There are Moslems and there are Christians. So one looks at the population and one would raise the question, what would be representation of this huge amount of Hindus that makes the most sense? Caste? In 1949, the caste system officially ended, but for the last 50 years, those of us who know a little bit about India know that it has residuals. The caste system isn't over.

So let's say one was going to do a large population study of India, and you wanted to talk about representativeness of the population. Would you use Brahman, Chitra, Dalit? Would you use those categories? And if you did, is there not some danger that you'd find allelic frequencies in those categories which coincided with those caste system categories?

Whoa! Now the question comes up right away, is the research reifying the taxonomic system that you thought you destroyed in 1949? People will raise the question, are

you going to use race, coming back home to the topic here for a moment, as a taxonomic system when, in fact, we know race as a category has all kinds of fluidity biologically, socially, anthropologically, politically and culturally? We know that. So once you use the notion of race and you're going to use genes, like the Dalits and Brahmans of India, are we not as researchers in danger of providing a kind of reification of that taxonomic system? So that's the question, that's the concern.

Surely, after 3,000 years of a caste system, where you only can marry inside of a particular caste, you'd find allelic frequency variations which were pretty common in certain groups and not in others. But when you interpreted those results, would you conclude that this was about genetics or rules of monogamy, heterogamy, endogamy, anthropological rules? Because the rules of engagement around sex in India are not so much about biology but about those cultural rules. The cultural rules produce allelic frequencies in castes A, B and C which turn out to maybe have outcomes for health.

I'm going back and forth between India and our own culture for obvious reasons, because we are clear when it comes to India that this might be problematic. We get a little bit foggy in our own country about this taxonomic system. I'll say in a few moments how this might be addressed. The relevance for the U.S. will become obvious.

What does it mean to have a population study as representative in the U.S.? We obviously want whites and blacks, we want Asians. We care less about Christians, Jews, Moslems and Hindus. Why? Because it's not part of the stratification system in our own conception of what's deeply embedded in the structure. That's not about biology. That's about social categories. We can say let's have a study which represents Christians, Moslems, Jews; you'd be laughed off the block here, but not in other places.

One half of all cancers occur among people living in industrialized parts of the world, one half of all cancers. This group constitutes one-fifth of the world's population. The World Health Organization collected data on cancer rates from 70 countries, and here's a direct quote from the WHO's study: "Eighty percent of all cancers are attributable to environmental influences." So step back for a moment and look at those two figures. Half of all cancers that we know about are occurring in one-fifth of the world's population, many in the industrialized world.

Now, migrant studies are among the most powerfully persuasive ones in sharpening the environmental sources of high incidences of cancer. Jewish women who migrate from North Africa, where breast cancer is rare, to Israel, a nation with a high incidence, (inaudible) that breast cancer risk is half of the Israeli counterparts. Within 30 years, African-born and Israeli-born Jews show identical cancer rates. One of the most compelling environmental studies of cancer ever conducted, researchers found an association which was significant between the use of cultural chemicals and cancer mortality in 1,497 rural communities.

A study that represents the population. Could we not have a study which represents those who live around toxic waste dumps and those who don't? A study that looks at those who are handling chemicals and those who don't? That is, it may not be that race or other kinds of social taxonomic differentiations is there. Maybe what these data are showing is that the representativeness of the population that's relevant to a health study on cancer could be what I think someone said in the earlier session, maybe has nothing to do with race, unless race puts you around a toxic waste dump.

The work of Julie Shay in New York City, her doctoral thesis about three years ago, what she found was that there were four important waste sites, and it turns out that the African American population was living much more around those waste sites than were upper middle class white people. No big surprise, but it does have some bearing on how you would design a study.

Now, if you're talking about genes and environment, that's the way this is being framed, it sounds kind of good. It sounds like we're going to look at genes and environment. But this table is not set evenly. The ones doing the research on the genetics of these kinds of problems, whether it's hypertension or cancer or you name it, it tends to be the notion that they're doing the really hard science. They're doing the close-up empirical work, and those doing work around toxic waste dumps, that's kind of epidemiological, soft, humanistic, not very focused, not hard data. And yet the data that would seem to me to be most compelling are the ones that I just gave you.

Where is the cancer rate in this country? It's around these various sites. So my concern, if you haven't quite figured this out, is that the framing of the study as genes and environment already is assuming that there's a kind of interaction here that's more or less equal. In fact, and I think empirically, one can say we've got good data that the environment is going to play a dominant role in many of these kinds of diseases, that genes will play some role, but that when we put it together it will sound like the real imprimatur of science is on the genetic side. What's the bearing of this? Well, I'll give you an example. I told you I could expand or collapse. I'm going to collapse here in a few minutes and open this up for a conversation.

The example is the one that most of you are already familiar with, the fact that we now have a particular market for a hypertension drug for African Americans. I'm not going to belabor the point, but I'm going to make the point in the following way. It's not so much about genes; it's about how one thinks about the problem.

If you find that a population of African Americans, or any ethnic group, has a higher rate of something, and then you find that there's some kind of a shift or an imputation of a shift in the bodies of those people, you'll say, well, it must be about their ethnic or racial category. Well, the work of some epidemiologists suggests that it does depend on whether or not you can do migrant studies or cross-cultural studies. So hypertension in the black community is high in this country, but if you go across and look at the work of Richard Cooper looking at eight different countries, three different continents, comparing hypertension among blacks and whites in these different countries, he finds that the differences either go away, certainly not clearly that it's racial.

In this country, staying only inside our own borders, looking at a national study, seeing high rates of hypertension among black people, we might say allelic frequencies seem to show that this is a more common phenomenon over here, and we might therefore make this huge mistake inside our own boundaries. If we look, however, at Brazil, at sub-Saharan Africa, at the Caribbean, as Cooper has done, and we show that these differences begin to shift around, then the whole enterprise looks very, very different.

Prostate cancer. I'll end with that. The black prostate cancer rate in this country is double that of the white prostate cancer rate. Let's say you do a national study and you find this, you find more national data indicating that it's the case, and you might find using computer technology that you would see allelic frequencies in the black population which were different from the white population. You might find that. It wouldn't surprise me at all.

However, to leap to the conclusion that the prostate cancer rates are a function of these differences in the genetic structure is a huge leap unless you have functional genomics. Well, we're some way away from that. So the question is going to be what do you make of these data? It goes back to the game of go. If at stage 1 you've decided that the taxonomic system you're going to deploy is using race, then how these data are reported out that you just heard becomes vital. As a social scientist, what deeply concerns me is that the table is set so that the genetic interpretation has the imprimatur of more power analytically when, in fact, the data set might indicate that if you went cross-cultural, cross-national, migrant studies, you'd have a different conclusion.

So my advice is expand this always to talk about migrant studies and cross-cultural, and include that in any kind of attempt to talk about a national study. Otherwise you've set into motion at stage 1 in the game of go, and you'll see where you'll wind up, with a reification of race.

Thank you.

DR. WILLARD: Thank you, Dr. Duster, and thanks to all three of you.

We'll now open it up to a roundtable discussion, and I'm going to turn it over to Ellen Fox, who is going to be leading this part of the session.

DR. FOX: Thank you. I'd like to add my thanks to the three panelists. You've certainly given us a lot to think about and talk about, so let's begin the conversation.

Yes, Kevin.

DR. FITZGERALD: I'd like just to throw something out to all three. Thank you, too, for your presentations. I'd like to start with Professor Duster, first of all because it's so rare that somebody uses go as a metaphor. So I'd like to build on that a little bit and draw it out just a little further, because even after you have chosen the first few moves that you're going to make to sort of set the pattern that you want to pursue, then comes in this constant tension between continuing to make the bold broad move or having to consolidate at some point to either attack or defend a smaller territory.

I'm wondering would that decision, though not normally done in the game, be better made in this case by committee or community than by an individual or, say, a small group? So to use what we've heard before, if we were to follow a sort of community engagement model as a first step, take the issues that you have raised, all of you, and put it in that particular context, what would you see would be the advantages or disadvantages to addressing those issues within that community engagement model?

DR. DUSTER: Well, as you heard in the previous session, community engagement is a very foggy and vague idea. What's the relevant community for African Americans? So what would be the community engagement around prostate cancer? Well, you might say, given the fact that you're talking about males, you've got a cut right away. You're going to talk about black males age 40 to 70. That's going to be the relevant community.

I mean, I do think it's possible for some of these kinds of things to be understood situationally and empirically. I don't think one can come at this necessarily with a kind of didactic axiomatic system where you say, okay, we're going to have the community -- who is the community? -- be determined by the kind of research. So that's my first answer to the question. I don't think community engagement is the answer. It's the beginning of a probe, a wedge, an entry into the relevance of the research, and then the question is, well, is the community sufficiently informed to pursue?

This is an old horse. People will say things like does the community know enough, the community of 40- to 70-year-old black males? A huge variation here. One of the things again is I'm drawing upon my experience in the ELSI working group. We had this discussion earlier in this session, but just to sort of crystallize it here again, one version was you educate people because they don't know genetics, and I thought Joan Scott was quite good about that. You educate people about the issues. You don't teach them Mendelian genetics. You teach them about the issues in genetics.

So what would you begin to tell people about a prostate cancer study? Unless you begin with what I thought was powerful evidence about the possible migratory features, the way in which the environment is playing a huge role, nutrition is playing a huge role. If you simply start looking at genes and environment, you're going to bring the community into a kind of a fog, and the scientists could say, well, we have good data indicating that prostate cancer is allelic frequency X, Y and Z. And what is the community going to say?

I mean, I think that the frame here is vital, and I'm not sure a community engagement is going to get us very far. But I'll let Pilar and Henry Greely respond if they want to.

DR. GREELY: I'm not sure this is community engagement exactly that I'm going to respond to your question with, and the only times I've tried to play go, the computer has crushed me on the simplest setting.

But I do think that there is a role in the creation of appropriate informed consent protocols and methods for preliminary discussions with communities and other research subjects, other potential research participants, to try to make sure that they understand the full meaning of what you're saying, and part of that is in a sense community consultation or community discussion to make sure that when you say these could be used by other researchers, that they understand how far that means; or if you say you won't have any control over subsequent uses, that they understand with some specific examples of what kinds of subsequent uses those might be.

So I guess I see it both as a possibility for discussing some of these consent issues with communities but also using that as a way to hone your consent process to make sure subsequently, when you put the consent process into play, that the people undergoing it truly, as best as you can guarantee, which of course is certainly less than 100 percent, but truly understand what you're telling them.

DR. DUSTER: Just a quick response. It occurs to me that maybe a better way of thinking about this is that maybe the community engagement that's relevant are those who live around toxic waste dumps, not blacks.

DR. OSSORIO: That was what I was going to say, actually, that I think Troy's comments really went to the question of exactly who are you going to engage, right? And I was a little concerned when I saw the kind of background paper that people were conceptualizing this project in kind of an old model and not thinking about the possibilities of gathering a lot of environmental information, gathering a lot of exposure information and how that actually cross-cuts a lot of these kind of simple-minded notions of race and genetic causation of disease.

So I agree with Troy, that when you think about whom to engage, I think it would be a failure if the engagements were just sort of done along the lines of racially organized communities.

DR. FOX: Next I have Julio, Muin, Joseph, then Jim.

DR. LICINIO: I'd like to thank the panelists for a really wonderful series of discussions. I have two considerations that I'd like to bring particularly to Pilar. If the other people want to talk, I think that's also fine. And I really appreciate all the comments about how there may be many confounding factors in the environment or social factors that may not lead to a clear association between a specific genetic allele and a disease, but let's say that that association is found. Then how do you handle this in the concept of informing people?

The two scenarios I'd like to ask you about are these. One is that most likely, almost certainly what you're going to find is a percentage risk that's attributable to that allele. So how do you tell somebody that they have a percentage risk for something? For example, if they have a 90 percent risk of having a fatal disease for which there is a curative treatment, there is not much to think about. But what about if they have a 50 percent risk for a disease that there is no clear-cut treatment? You go around telling people they have a 1 percent risk of having this. What does it mean? Where is the cutoff and who determines that cutoff? Over what timespan? So that's kind of one line of questions.

The other is that I was in a very thought-provoking panel at the Kennedy School of Government on genetics and the law, which is exactly your area. The thing that is apparently a very hot topic now, and I don't think it's been dealt with very much here, is the issue of the genetic testing by proxy. It's basically obtaining genetic information about somebody without testing that person, but by testing a relative.

Just as an illustrative example, the BTK killer was apprehended because of a match between the DNA found in one of his victims and the DNA of his daughter, who did not give consent for DNA testing relating to any type of criminal investigation. Her DNA happened to be in a database.

So what about this issue applied to this project? This could be very farfetched and removed, but let's say if a member of the project goes missing and then a body is found, do you use the DNA that you have from the project to identify that person? Or what if the person is in the Empire State Building, there is a new terrorist attack, that building collapsed, you have a charred body and you know that the person potentially was in the study, and you want to check?

Then if you check, let's say, and it's not the person, but there is a kinship match and the search continues and it's found that the person's DNA is actually in a crime scene. So you know that the crime was committed by a sibling of that person.

Where do you stop? It sounds almost cruel, let's say, if a member of the study goes missing and a body is found, and it's natural to try to do the thing, but if you don't do it, I think it's problematic, since you have the DNA stored. If you do it, usually things unpredictable do happen, and if something like this happens, it can put the credibility of the study at large at risk.

So how can we address these two issues?

DR. OSSORIO: Well, the issue of finding alleles for which it looks valid and you have the statistics to say there is a 5 percent probability that if you have this allele, you'll develop X outcome, first of all, that would definitely not fall into the category of information probably that anybody would think it's obligatory to report that back.

So you would be in a range of permissibility and perhaps fairly low if you're talking about a range that is trying to be attentive to the seriousness of the condition and the

importance of this information in managing somebody's medical care. Knowing that you have an allele that puts you at just a slightly increased risk for a common complex disease probably is not going to be the kind of thing that you'd put very high on your priority list for reporting back information.

Some people have said, well, you should report back anything that's clinically relevant. I think it would be incredibly difficult to do a study where you involve 500,000 or 1 million people and have that kind of regime where you're reporting back anything that's medically relevant. The economic burden of doing that would be so high, just for one thing.

So, number one, I think there's a range of permissibility, and some of these things that have only a slight predictive value would be the things that you'd put in the category of not reporting back.

How you make that decision, you know, there are a lot of different ways to make it. One of my suggestions is that that is the kind of decision that you might make, at least in part, in some kind of community engagement, and I think, for instance, the reproductive, things that have sort of carrier status, reproductive relevance, I suspect that if we did engagements, we would find out that for a lot of people that is very important information and that if we can give it to them, they would like to get it from us and that they would give that a much higher priority. If we say that there's going to be a limited set of things that we will report back and we have some choices to make, participants can help us make those choices.

Also, we can give participants a range of choices. Some people won't want any of it back and certainly wouldn't want back things that don't really affect clinical management or something like that.

But I agree. There are lots of choices like that that will have to be made.

Also, something I didn't talk about, is that there will still be unexpected things that come up. For instance, if you're a researcher doing follow-on research and you don't have the linking information, which will probably apply to a lot of people, and you find something that it turns out is very significant and wasn't really anticipated by you when you started the project, and you didn't go back and get additional informed consent, and now you feel, oh, gosh, it does fall into that category of things that we've said should be reported back, those are the unusual situations that should go back to the IRB to develop a process for contacting a person and doing that. So there will always be some adjustments that you have to make on the fly.

The second question of the non-medical uses of this kind of a database, I mean, part of this has to do with the data access policy and what kind of policy you have upfront. The idea that you would give out data to parties who have IRB approval on the face would rule out a lot of these non-medical uses or law enforcement uses, but if they wanted to subpoena or they wanted to get a court order to open up your database or get access to your data, in some cases they certainly might be able to do it. I don't know to what extent a certificate of confidentiality would really work in this kind of a case, but it might.

You know, what I wanted to say, though, was that what Kathleen said to you earlier on is very true. In those communities that are -- and you know this, right? -- disproportionately targeted for stops and arrests by the police, there is an incredible concern about law enforcement having access to these things.

Both Hank and I, and I think Troy as well, have been working at various

times as part of a project at the Kennedy School where they're looking at law enforcement uses of genetics, and the things that the FBI wants to do with genetic testing, they're way out there. They would love to be able to get all kinds of genetic information from people.

It's interesting that there are provisions in the law to use law enforcement databases to do identifications in situations like another terrorist attack. Some state laws would perhaps protect a research database against being used for other purposes in many cases, but not all state laws would. So there certainly is a legal area where it would have to be a policy, some kind of policy, of the project and of the NIH or of HHS that would set those limits.

DR. LICINIO: But that would have to be set a priori.

DR. OSSORIO: Yes.

DR. LICINIO: And just to endorse what you said, in our community project in Los Angeles in the Hispanic community, the first issue that was raised was is this is going to be used for law enforcement? But because our collection is anonymized, so we completely don't know who it is, that issue is not applicable, but it is here.

The last comment is that if you really have this possibility that the sample could be court ordered, which was the case, actually, in the BTK example that I gave, should you put that in the consent form upfront that it's anonymous, but these records could be obtained by court order and we cannot stop this from happening?

MR. GREELY: You have to, I think. You've got to be honest and there's no way, even with a certificate of confidentiality, that you can necessarily guarantee that a court order won't be issued. The specific example that I think is most likely to breach a certificate of confidentiality is when a criminal defendant can make an argument that this information is crucial to his defense and he has a constitutional right to it, and the Constitution trumps a mere statute or regulation.

So if, for example, with a criminal defendant, there's other DNA found at the crime scene and he can show that it matches an anonymized sequence in this database, I think he has a very good argument that he has a constitutional right to get that identity regardless of whether or not there's a certificate of confidentiality.

In that case, you've got to tell people upfront we cannot promise you complete confidentiality, and here are some of the ways in which that confidentiality might be breached beyond our control.

DR. FOX: Thank you.

I have six people on my list. You're next, Muin.

DR. KHOURY: I'd like to thank the speakers this afternoon.

It may be the lateness of the hour or sort of my own fog here, but I'm looking a little bit for more clarity around a couple of areas, and I think Dr. Duster challenged my mind to think harder than usual around two areas. The first area is around representativeness and how you cut such a study by religion, group, ethnicity, et cetera. The other area is genes and environment. I'd like to throw back these things at you so that you can help me with more clarity.

As a primer to this, I'm a public health professional. I spend a lot -- actually, all my time and career collecting data on populations from a public health perspective.

Ideally, if you want a population sample that represents the whole U.S. population -- and assume we have 300 million people that live here -- and you want a 1 million person sample, you have a line listing and you pick every 300th person. You'll have a totally

representative sample of the U.S. population, completely random. Then you can post-hoc study which group, which religion, whether they live in toxic dump sites, whether they live in rural or urban areas, whether they live in State X, State Y, or Z. That's sort of the completely random approach to public health research that we've used.

Unfortunately, because minority groups are minority groups, a complete random sample doesn't do us a service. So we've done a lot of tricks in public health to do what we call the stratified random sample. We go enrich the sampling scheme with sort of the minority groups.

But there is no limit to how much you can do that cutting. I mean, right now, we do it by race and ethnicity because of the health disparities around that area, but when you start doing it by state, by county -- you have 50 states, 3,000 counties, rural versus urban, zip codes, toxic dump sites, et cetera, migrant versus non-migrant -- you know, it gets a bit more complicated. So maybe you can help me with a bit more clarity.

The other issue is around genes and environment. I think it should be obvious to everyone that a study like this, if it was only based on genes, it's not worth doing because using appropriately collected case/control studies, you can look at the genetic contributions of all diseases because genetic variants don't change. You measure them once and that's it. You don't need to do a cohort study.

I would say the major impetus for such a resource or a national project would be to look at genes in the context of environments, and we all know the complexity of measuring the environments, although we're making major progress in measuring toxic chemicals in the serum and the blood and the urine and all of these things. Some of it is tough, like measuring social environment.

This reminded me. You know, at some point you said that 80 percent of cancer is environmental. To me, it doesn't imply that the other 20 percent is genetic, because one famous epidemiologist many years ago said, "We can easily show that 100 percent of a disease is environmental and the same 100 percent is genetic as well," because all of it is due to gene/environment interaction.

So if there is anything to be gained by a resource like this, you'll have to get sort of the balanced view of measuring genes and measuring the environments, and doing the appropriate sampling scheme that would allow us to get the most pragmatic sample of the U.S. population to allow generalizability of results.

So given what I just said, maybe you can repackage what you said earlier and help me see how what you said can change my way of thinking, because I think there are some gems there that I would like to get at the table, and anybody else who wants to respond is welcome.

DR. DUSTER: No, I don't think I have any gems. I mean, I think the message that I want to deliver is that this early stage of framing of the project is so vital that we need around the table some understanding not just of the genes/environment, but how the genes/environment interaction is going to be reported out, how the data are going to be collected, and that can't be done by a group like this.

That's simply a cautionary tale, and what I was suggesting is that one way to think about it is the kind of work that Cooper does. You're talking about race and genetics, boy, that's already volatile. So let's talk about race in four or five different countries and see whether or not the rate of hypertension or prostate cancer or breast cancer among Groups A, B, and C

changes.

That's a different kind of study than a national study. A national study in some ways I think reduces your capacity to tease out the genes/environment issue. I mean, that's an old argument and we shouldn't go down that road. You know, one should never say "genes and environment." It's always interactional, but we're going to just parcel that out.

DR. KHOURY: Pilar?

DR. OSSORIO: You know, when I try to think about this in great detail, like what would be the best sampling strategy, I just get myself really bamboozled. Part of it I think is that those questions would be easier to answer if there was some particular medical focus, so that understanding how to do the stratification, it might matter whether you want to first look more at cancers or first look more at heart disease. That might actually change the optimal way to do the stratification.

I'm now way outside my area of expertise, but I know that in discussions with NCI a few years back, one of the issues that came up was that different collections of tissues and information are better suited to answering particular questions. In that case, they were talking about there are reasons to go ahead and do new large studies, make new large collections.

Again, there are some choices to be made about how much this resource is going to be very broadly applicable and how much it might, if you focus towards a particular set of conditions, that might influence the stratification scheme that you would use.

You know, we had some discussions this morning about interdisciplinary work and so forth. In my own sort of discussions with people about how to develop a project that could really measure interaction better, I'm constantly struck by the fact that there are, for instance, out there data sets that are longitudinal that go back decades about air quality and certain pollutants in the air that go across the United States zip code by zip code that could be married to medical information and genetic data. There actually are a lot of environmental data sets already out there that it's worth trying to figure out what they are and how they've been collected because that might actually, if we really wanted to be serious about collecting environmental information, help guide some kinds of sampling schemes.

DR. FOX: Jim Evans?

DR. EVANS: This was a great panel. I learned a lot.

One of the things that's worthwhile being reminded of as a geneticist is that it is definitely true that most of the maladies that afflict us are more environmental than they are genetic, and I think that if we are going to look at genetic/environment interactions, we have to be as diligent in our methods for looking at environmental influences as we are about genetics.

My question is for Professor Greely. I think you pointed out something really important, which is that truly informed consent in this situation is impossible. In fact, there are those who would argue that truly informed consent is almost always neither, even in a clinical situation, and that what makes it work, what makes the interaction work, say, in a clinical situation or, perhaps in a more abstract sense, the research situation, is one of trust, that if there is trust between the practitioner and the patient or the researcher and the participant, then those issues are much easier to get around. I think that underscores everything we've been talking about about openness and having some degree of trust.

My question for you is it seemed like you were talking mostly in the issue of opting out. You know, what kind of control a participant has. In trying to decide those things

upfront, isn't there a huge role if you can maintain contact, which you would have to do anyway? If you can continue to inform participants in aggregate about the research projects that are going on?

Do you think that's a viable kind of solution to much of that problem to allow people to give very generally consent initially, which I think we all agree at some level is necessary for such studies, but then to opt out if they see that, okay, there's a project planned that raises problems in my mind, et cetera? Would that be a way of addressing it?

MR. GREELY: It would be a way and it would be a way that's better than the current system. I don't think it would be the way I would most recommend.

First, I do think we should talk about this initial interaction of the research participant as more, in this context, permission than consent. It's useful to use a different word to separate it entirely from the concept of informed consent, which, though it can never be done perfectly, can almost always be done better than it can be in the context of one of these multi-use, multi-decadal resources.

The idea of maintaining communication is I think an excellent one, and trying to inform the subjects, the participants, of what things might be done with their DNA and their data is a useful one, and I think that will help you with sort of intermediate ones, intermediate issues where you wouldn't really think that anybody is going to be all that concerned about it, but it turns out you've got four research participants who really are quite troubled by research into pancreatitis. You had no reason to suspect that was the case, but by golly, they are and they read about it in the newsletter, and so they objected. The newsletter told them if you object to any of this, please let us know, et cetera.

My problem with it is if you get into ones that are more clearly controversial, where people are more likely to object, the difficulties of maintaining real contact with people are so great and in recontacting people six months later, you lose a large chunk of people. A year later, you lose a bigger chunk of people. Then -- and here I'm speaking from anecdotal, personal, empirical experience -- the odds that any piece of mail is going to get into the trash can without being read are fairly high in most households, I think.

So if it's something that you've got reason to believe a significant chunk of your population really might be concerned about, I don't think the information plus opt out is sufficient, because some of the people won't get the information or won't read it, won't realize it, won't take the opportunity to opt out, and if you later tell them, hey, we told you about it and you had an opportunity, they're still going to feel misused.

DR. FOX: I think we have time for the last three I have on my list.

Cindy?

MS. BERRY: Muin was actually getting at what I was thinking about and articulated it far better than I. I would like to make one more point for clarification for lay people like myself.

It's directed to Dr. Duster. Am I correct in assuming that the dangers that you are speaking of are not so much in the fact of collecting data and including a representative sample of individuals throughout the country -- I mean, we always hear at our meetings that it's important to include women and it's important to include different racial groups and have a good mix because it does nobody any good if we just have a bunch of 20- to 40-year-old white males. What good is that? We have to have everybody represented.

But that the real danger is really more in the interpretation of the data once

it's been collected and the types of studies that are embarked upon using that data? Because I don't know that just having a lot of different people from urban areas and rural areas and different racial groups in and of itself is problematic. It's more what people do with it and the jump-to-conclusion type of results.

Am I correct in assuming that or are you saying that at the very beginning --

DR. DUSTER: Both. Both things are true. I think how it's reported out is vitally important. How one interprets these data on, let's say, prostate cancer and race, that's the reporting out problem.

But having shaped the study and framed it in terms of these categories is itself the problem of go. That is, once you've said we're going to separate people based upon race and then come at them with an understanding of different allelic frequency patterns, there's a tendency to believe that those frequency patterns are in that racial group, whether they are or not. You see?

Now, one could say empirically that that will be sorted out. Over the next 30, 40 years, we'll find out.

But in the interim, there tends to be a reporting out which says -- let's take the example I used earlier. Blacks actually may have a different kind of allelic frequency than whites who have prostate cancer, but we don't know if there's functional outcome. We just know that that's the pattern. In the interim, the reporting out is going to sound like it must be genetic.

MS. BERRY: But isn't the problem more in the prostate cancer study or the person who is trying to reach those conclusions as opposed to just the fact of getting people to participate in the large population study?

DR. DUSTER: Well, if we leave and go to the caste system, I think it becomes clear. Right? You'd say, oh, why would you think that people from different castes would have different genetic makeups? Well, because they married each other for over 3,000 years. That's why you might think that, but would you think that therefore that had an impact on their prostate cancer rate?

That is, having set it up to collect data by caste, you've already prefigured the capacity to report out certain things. That's why the two are related. It's not just collecting data. It's collecting data by certain social categories, and societies being stratified, it's inevitable that the allelic frequencies are going to reflect that as well. So the danger is going to be genetic interpretation of stratification.

MS. BERRY: But just to play devil's advocate, is there something wrong inherently, are you saying, with including all of these different groups and factors? For example, race, gender, ethnicity, all of those things? To me, it just seems that the danger is in what you do with that and the conclusions you reach.

DR. DUSTER: I think that's right. I agree with you completely. It's in the conclusions and the reporting out.

What I was pointing out was something at the very outset of the study, which is why I went to the caste system to make the case. It becomes clear in the caste system that there's a real danger if you begin to do genetic studies in that system, people will say you're recreating the very taxonomy we thought we got rid of in 1949. That is, you give a kind of reality to the allelic frequencies, which are going to be there. I mean, if Brahmans have been marrying each other for 3,000 years, there are going to be certain patterns there. But what do

you do with it when it comes to health outcomes?

DR. OSSORIO: If I could just add a little bit to that, I think one thing is to be really clear about what your notion of representation is and why it's important. I frankly think that part of the reason it's important to have broad representation with respect to race and gender and so forth is not necessarily to achieve a particular scientific goal, but because this is a huge project potentially in which millions and millions and millions of federal dollars will be spent and those categories are politically important, and there are disparities of all kinds, including health disparities, that map on to those categories, and that participation is a political way of saying to people you are important, you matter, your needs matter.

It might perfectly well be that if you did a study with, say, only white people looking at the ones who lived right near toxic waste dumps and the ones who lived out in pristine wherever, you might find a gene/environment interaction that's absolutely generalizable to anybody who has a particular set of alleles and a particular set of exposures over their lifetime. It might be perfectly generalizable to all those people who weren't included or many of them. It might be a very important one.

Even if that were true, I still think that it's very important to have representation in the political sense, and then there are also scientific reasons to have people with different exposures and different life experiences and of sort of the greatest amount of genetic variation that you can. To the extent that you're using things like race and ethnicity to try and expand the amount of variation that you've got in there to study, there is a scientific justification for that.

But part of what happens is that we sort of collapse every reason for inclusion into some kind of notion that's very deep in our culture that races are genetically distinct groups of people and when you see differences between races or ethnic groups, in some cases, there's a genetic cause, and we don't get much beyond that.

I think this project or some project of this sort has the opportunity to break down some of these kind of simpleminded ideas, but part of that is thinking what kinds of data would you collect about people. Not just are we going to go rural, urban, whatever, but what other kinds of information are you going to collect about them that will help you understand the gene/environment interactions so that you're not just left at the end with analyzing your data based on race and gender?

DR. FOX: We have only three minutes left in our scheduled session, so if I can ask folks to keep your questions and answers brief.

Debra?

DR. LEONARD: Actually, I realize that we're going to be having a general discussion about this, and my question is more relevant to the SACGHS members than the panel. So I'll hold.

DR. FOX: Michael Carome?

DR. CAROME: Hi. Mike Carome from the Office of Human Research Protections. Some of the comments I've heard seem to presume that the research studies that are going to be used and this database that's going to be created are all going to have IRB review, and I presume that's based on the assumption that the regulations are going to require such review.

I think it's important to note that some guidance has come out of our office involving use of coded private information or coded biologic specimens actually can be done in

a way in which the recipient of those specimens and the data can't readily ascertain the identity of the individuals to whom that data and specimens pertain, and therefore, under the regulations, that research doesn't involve human subjects, and therefore that research doesn't necessarily need any further IRB review or any more informed consent process or exchange of information with the subjects.

I just think the group needs to be clear about that. It doesn't mean you couldn't impose some ethical review -- call it IRB review or some other review -- for any uses of it, and that's probably a reasonable ethical consideration, but it may not be based upon a regulatory requirement. I just wondered if the group had any reaction to our guidance on this topic and whether they find it to be problematic, given the type of research being proposed.

MR. GREELY: I would hope that such a resource would include as a condition, contractual or otherwise, for the use of its data IRB or IRB-like review. I would also hope that IRBs, though recognizing that it might not technically be human subjects research and might not technically be something that they're required to review, would be willing to review it.

The broader question about your guidance I do find is a much longer story than we have time for, but I'll just say I do find it somewhat problematic, particularly because of the limitations on confidentiality and anonymity that I talked about earlier.

DR. FOX: Thanks to all the panelists, and that ends our roundtable discussion.

DR. WILLARD: Thank you, Ellen, and thank you all three of the panelists and, by extension, the whole day's worth of speakers. It's been tremendously educational for all of us and we appreciate your contributions and your being here.

So we now have I guess 45 minutes for the committee to have a discussion to address next steps, to digest what we've heard today, and hopefully distill that down to what we've learned today and how that impacts the kind of issues we would like to tackle in a report which would be transmitted eventually to the Secretary.

I have some thoughts, but I think I'll hold those for the time being and simply see if other committee members want to start off a conversation. Debra?

DR. LEONARD: I'll start off being a little controversial. In listening to all the sessions we've had on large population studies, it seems to me that this project is much bigger than NHGRI or the NIH, and that right now it's coming from a science, even a genetics, perspective and could get into a lot of trouble. I'm concerned that NHGRI is not engaging the expertise or resources of the other relevant agencies -- CDC, AHRQ, HRSA, EPA, and other agencies that I don't even know the initials of who may be relevant to this project -- and I think that these agencies have a lot to contribute, if not being essential, to the success of the project.

So I was wondering if the other members of SACGHS were feeling the same way and maybe what we need to request is for something from the agencies as a group to come to us with a plan of how to better work together, rather than this having to be solely an NHGRI-driven initiative.

DR. KHOURY: Just to correct Debra, and I'm sure Francis will add to this, there have been several contributions from members of CDC for that report that you see.

I think the way I look at this is that right now, if we think about this as a research study that's going to involve 500,000 people to be collected on genes and environmental factors and be followed up over time, that's sort of one issue, and I think there

has been a lot of thoughtful comments and discussion from the group that Francis assembled, which involves multiple agency representatives as well as the scientific community at large.

I think the implementation of where we want to go next, if we think of it as a national resource, then I think the advice that this group can give to the Department is about a study that's in the context of the general translation of genome science into population benefits, because this is the first time that we are embarking on a study that's beyond the test tube, beyond gene sequencing, and trying to figure out what genes mean for the health of people who live in Michigan or Hawaii or wherever, and then figure out how to use that information for prevention and treatment and medicine in general.

So I think as you all deliberate in your discussion here, think about the context. Think about not only a study in a particular time, but as part of an initiative that the various HHS agencies can rally around, because we all have slightly different missions, but other than NIH, we're all in one shape or form or some iteration into the process of translation, of translating the basic science that NIH sponsors and produces into population health benefits.

So we've heard, for example, throughout the day a lot of issues around the community engagement, the education of the public, the public policy issues, the ELSIs and, in a larger context, the involvement of state health departments and the convening power of public health, because at the end of the day, this is a public health research endeavor, because it purports to generalize the finding of a series of studies under a big banner into what it means to the health of communities.

I mean, the whole Human Genome Project was done with the blood of one or two people or under 10. Here we're talking about basically a lot of people coming together.

So there are all these issues that will have to be weighed in and discussed by the committee as you produce your final report. As you said earlier, the report is not going to reflect the scientific merit of the study, but the broad policy and public implication of a study like this in the context of the current health system as we know it today.

One thing that I'm sure the committee does not want to end up with is by widening the gap between the research enterprise in genomics and the application enterprise in genomics because right now the gap is large in the sense that there is a lot of public and private resources going to discovering genes, both from NIH and the private sector, but very little in the context of translation, and if you want make a real impact, I think that view should be a little bit more balanced than providing advice on one study in one given point of time.

DR. WILLARD: I'm going to go to Francis just because it specifically deals with NIH.

DR. COLLINS: Briefly, again, I'd like to reassure Debra that there is no expectation at all that if a project of this sort were ever to actually get off the ground that it would be run by NHGRI.

This was sort of a difficult circumstance this morning. I found myself probably talking too much and defending the project in part because we didn't have in the room a lot of the people that were involved in that year-long study that had generated a lot of the study design considerations, most of whom were actually not from the government. They were scientists of various expertises in the extramural community.

NHGRI's role so far I think has been to be sort of a convener to try to get people to think about this and the scientific opportunity kinds of questions that come out of it, but if this were to get underway, it would never succeed without the full participation and a

partnership of many of the government agencies that are represented around this table, and some that are not, like EPA, for instance.

Furthermore, I think there would need to be significant partnership opportunities explored with the private sector because it's the kind of data that they're also very interested in and potentially might be willing to help cover part of the cost.

So as far as, if it were to get off the ground, where would it be located, I have no idea. Would it be at NIH? Would it be somewhere else? If it was at NIH, would it be in one of the institutes that's used to doing large studies, like the Cancer Institute or Heart, Lung, and Blood Institute? Maybe. Would it be in the Director's Office? I have no idea. We're nowhere near the point of beginning to think about those issues.

DR. WILLARD: Kevin?

DR. FITZGERALD: I thank Francis for this because it was a great segue right into I think you're absolutely right, all those groups would have to be involved, but I think if there's one thing we heard that was at least clear to me today, if this goes anywhere, it has to have the public engagement. This has no traction without the public. It is a public health issue. The public has to be on board.

I mean, we can leave it up to somebody else. We can leave it up to the Secretary to bring in more experts to decide exactly how to go about that, but I think if there's anything that we suggest along with this, the one thing we did hear clearly is not only does the public have to be engaged, it has to be engaged immediately and be part of the process all the way through.

The points that the bioethicists brought up, at least Hank and Pilar, is this feedback question. Well, if there's continual conversation with the public, I think in many ways that at least mitigates that issue to a significant extent. If we have structures in place to continually get feedback from this constructive engagement, then I think that helps certainly address a lot of those issues.

DR. WILLARD: Other comments? Jim?

DR. EVANS: Yes, I was just thinking that it would be helpful to get some data or get some expert opinion on the feasibility in the broadest sense, given the fact that we're talking about a prospective study of a huge number of people in an environment in which, I think Joann Boughman put it nicely, we have a very fractious health care system.

I know from personal experience that trying to keep up with people in a large study, much smaller than this, is extraordinarily problematic, and if we were in New Zealand, I think the question would be different and the question would be much easier, and I think it might be worth getting some expert advice about just the simple feasibility in a broad sense of this kind of thing in this country with our health care system and its balkanized nature.

DR. WILLARD: You could ask the IRS. They have experience in this country.

(Laughter.)

DR. EVANS: Yes, they can track people down pretty well.

DR. WILLARD: Debra?

DR. LEONARD: Jim and I were talking at one of the breaks and it does seem astounding how many things, issues, would be addressed and so much easier if there were a national health care plan. That doesn't seem within our purview to make comment on, but it's something that, having sat on this committee long enough and listened to SACGT also, it just

keeps raising its head, and can we just ignore it? Or can we not ignore it, I guess, is my question?

DR. WILLARD: Well, we can certainly put anything in the report we wish to point out what may be obvious already to the Secretary that that makes it more difficult to mount a study like this in this country than in other countries. I don't think we can recommend to him that he change it suddenly, but we can certainly point that out.

DR. LICINIO: In that spirit, I'd like to ask Francis what's the difference, although obviously it's like two different countries, but in terms of what we propose to do, between this and DeCODE, with the commercial issues aside?

DR. COLLINS: Well, the commercial issue is a pretty significant one to set aside. Well, obviously it's a very different population. What you learn about the role of genes and environment in Iceland may or may not map nicely across to somebody living in L.A. I think if we really want to understand those interactions, you need to apply across a broader and more heterogeneous group than what you're going to get from that somewhat exceptional part of the world, even though I'm sure a lot of very interesting things will come out of that.

But the other obvious one is the whole idea of data access. The intention of a U.S. study, as I think most of us have talked about it today, would be that this would be a data set that lots of people with ideas would have access to and they could intersect what you learn from environmental and clinical and genetic exposures with other kinds of data that are coming out of our advances in biology. That just empowers a much greater opportunity for things to be developed that are going to be useful and exciting.

Let me just say, I was a little worried about Jim's comment that we don't know how to do this. Again, I'm not an epidemiologist, but I've gotten to know a lot of them over the course of the last year and a half, and we do studies like this. Not at this scale, but look at the Multi-Ethnic Study of Atherosclerosis, for instance, MESA, following not anywhere near this number of people, but having all of those same problems and having pretty good success in terms of enrollment, in terms of ongoing participation and being able to do the follow-ups. Look at Jackson Heart. There are lots of experiences at NIH that make one believe it is possible to do this, although it's going to be hard.

DR. WILLARD: What's the scale difference, Francis, just for everyone's benefit?

DR. COLLINS: About a factor of 20.

DR. WILLARD: Kevin?

DR. FITZGERALD: Just to respond to what Debra was saying before, too, earlier in the day Francis pointed out that we might have some infrastructure challenges, but that pursuing a project like this could help one get the inertia to surmount some of those infrastructure challenges.

Similarly, engagement of the public, even just initially to just even think about the possibility of doing this, could also give you some inertia to address certain other particular infrastructure challenges, such as the lack of a non-fractured public health care system.

So many things could come out of this that would be good, not necessarily the specific ones that we're targeting, but again, that's the beauty of engaging the public.

Again, as I pointed out, too, in that one question that I asked and wanted everybody to be sure, also disappointments can come out of this. The public could say no.

That's certainly a possibility. That's all part of the beauty of that kind of engagement.

DR. WILLARD: Joseph?

DR. TELFAIR: Sort of an observation and a question. If we look at the report, Hunt, that you did earlier about where we on the subcommittee agreed to stop and we look at what the nature of the discussion was today, that's kind of where we took off in the discussion. That's an observation.

So that means that do we go back, then, and reconsider that information in terms of should we begin to start talking more in detail about those things? Should we find another way to kind of move forward with the things that we said to stop? I'm thinking in terms of next steps and a work plan, since that is what our charge is right now is to do, but I'm just observing that we did a lot of work. Granted, I should say the committee did, because I came in late to the committee, so I'll have to have truth in advertising, but it still seems to me that a lot of what was discussed today is sort of next steps.

DR. WILLARD: I think we have before us the opportunity to do whatever we'd like. I mean, we could, within the context of the prioritization process, decide that this was the only important issue we have left before us and that we should spend the next year addressing this issue. At the other extreme, we could stop now and simply say that after having spent two meetings' worth or parts of two meetings' worth being brought up to a certain level of knowledge and understanding and sensitization around certain issues that we're now ready to sit down and write up a report as we did on the reimbursement issue and share those thoughts that we have with the Secretary or anywhere in between.

So a good question to ask of the group now is are there particular issues that we either heard about today or didn't hear about today that we feel are so important that we need to hear about them again in some future meeting? Or do we feel that we actually have had a fairly good, broad discussion of many of the policy and process issues sufficient for us to then go ahead and say something intelligent, or hopefully intelligent, to the Secretary?

Sylvia, and then Joseph.

MS. AU: I think I would like to try to have a report, and this is going to be difficult, that simply describes the complexity of this project or this proposal with the recommendation that the only way to do this is with this community consultation process as the starting point to see how the public responds and what they want to do and how they want to do it. So I don't know if we can simply describe this complex project in just simple terms with that strong recommendation. I don't want to bog the report down in too many recommendations. I want the Secretary to realize how strongly we feel about community input.

DR. TELFAIR: I was actually going to say something similar, but actually a little bit more expanded than that, because it seemed to me that if we listen to everything that was talked about today, that there's a taking off point on a lot of these things. It seems to me that the more instructive thing to do is not only to talk about the issue of public engagement, which is a key issue, but in each one of these areas where people presented, to me there was a lot of commonality in what was being recommended.

It seems to me if we take that information and condense it into where we stopped and said here's what we understand about the key issues that we talked about, here are the common things that everyone's recommended, and here would be recommended next steps on how to address these things.

It may be that we as a committee cannot do that in a very short period of

time. We may have to go back and do some more consultation or discussion on it, but in terms of being instructive and to really take this and make it a dynamic document that is actually practical and you can see that it has some legs to it, I think that one of the things to do would be to really think seriously and seriously review what has been told to us and come up with some real strong ways to really get it done.

That seems to me to make the most sense right now if we take everything we said today in terms of next steps. That would be my recommendation. That's kind of in the middle of what you're talking about, but I'm a person who's a bridger, so I always look for the middle, because I think the middle is very, very doable most of the time.

DR. WILLARD: Well, certainly one possibility, and either Amanda or Sarah or someone will tell me if I have the words wrong, but one option is to allow a small group, which I think is called a work group, which includes not only members of the committee, but also allows us to take advantage of some of the expertise from some of our panelists today, and do essentially what you said, to assume that our notetaking was insufficient in and of itself, so we might need some more expertise ongoing to help us draft the report as opposed to simply turning to poor Amanda and saying go to it and let us know when you're done.

Amanda's been great up until now, as we all know, those of us who were on the task force, but this would be a slightly more expanded way to drill down a little more deeply on some of the issues that we heard about today.

DR. TELFAIR: Well, I would recommend that if it's amenable to the group, because it seems to me that that's something very concrete we can do. I would recommend it to the committee. If the committee was amenable to that, it seems to me to make a lot of sense, and I would recommend that or put it on the table as a recommendation for where to go.

DR. WILLARD: Before opening this up to the full committee, let me just ask Sarah whether I have that right. Is that something that we have the option of doing and do we have to take any special action in order to do something like that?

MS. CARR: No, you can do that. In fact, I'm not sure, I think your task force could involve other people. So we could continue to call it a task force, but it would be governed by rules of working groups.

DR. WILLARD: So let me open it up. Suzanne?

DR. FEETHAM: In listening to the discussion, which was very profound and outstanding today as we've all acknowledged, but what I'm hearing now in the discussion of next steps is the reinforcement of the complexities and the challenges, and I think part of the discussion as we move forward in next steps is the potential of this and the rewards of this and why it's so significant to the potential health of the country over the next decades, and I think that should be part of our framework as the so what, and yes, we have to deal with all of the issues that were so eloquently presented today, but I think that's the context we need as we move forward with this.

DR. WILLARD: Muin?

DR. KHOURY: I think it might be quite useful, before we throw it back to the task force, of which I'm a member, to try to kind of have a general discussion, as we are having right now, to get the committee members to say -- I mean, to have sort of a roundtable to have the two or three top recommendations that if you were to address the HHS Secretary today, what would they be? Then the task force would take that in the context of all the stuff that we heard today and then digest it into some kind of a document, because at the end of the

day, we know the complexities, but what we want is something that you guys will take our boss and tell him HHS should do A, B, and C, just like the way we took the reimbursement report, and then we can backtrack.

Now, if there are gaps or holes that would not allow us to make these kinds of at least draft recommendations, then we can go back to the committee or the task force and then rehash it a couple of times iteratively and come up with this.

But it would it be nice to get the members to say, okay, if I'm in the same room with the HHS Secretary today, what would I tell him around this issue?

DR. WILLARD: I would actually back up. There are two issues I'd like to go around to committee members and get everyone to comment on, and that would be one of them. What are the two or three leading issues that everyone can identify based on what they've heard and read?

But I think before I got to that, I think it's necessary to get a sense of the committee on level of enthusiasm, because there are actually many, many ways to write the report, but there are two sides to it. One is simply to throw the hands up and simply tell the Secretary and say this is the most complex thing I could ever imagine and you're going to have to reinvent the U.S. government system and the health care system, and God bless you.

(Laughter.)

DR. WILLARD: But good luck to you because this is an incredibly complicated issue, and by the way, here are some of the processes and mechanisms we think you may want to consider.

The other is to come at it -- and again, there's plenty of ground in the middle, so I'm overstating both extremes here for purpose. The opposite is to frame it the way I believe Suzanne was suggesting, which is to make sure that we're pointing out that there's a tremendous upside if we could figure a way to do it. If he could figure a way to do it, there's a tremendous upside here, and that we as a committee are very enthusiastic about it, or change the "very" word depending on each of our own feelings.

In order to give him that sense of recommendation, I don't think we necessarily need to either put our stamp of approval on this or not, but we could, and that depends in large measure on the sense of the group and on the level of enthusiasm for this before we then would necessarily go and identify the issues. I think it would help the writers of the report bring a report back to this committee, which is likely to be representative of the entire group.

So I'd like to go around and get a sense, and we don't need long speeches here, but we do need some sense of the committee members on a level of enthusiasm and level of feasibility to this whole challenge and whether this is something that we should urge the HHS Secretary to take on as a matter of some priority or whether this is something we're a little less enthusiastic about because of its extraordinary complexity and because of the depth of the issues that have already been identified.

So I'm looking on both sides, but since my body is turned in Joseph's direction, we'll start at your end, Joseph, and work our way around.

DR. TELFAIR: I would agree with Debra that it's a very complex proposal and body of work, but at the same time, it seems to me that we've looked through a lot of the issues around it, and I think with a little bit more review, I would be able to make a real decision. I'm highly enthused about looking a little bit more deeper at some of the more

complex issues in terms of feasibility. That's what I would be enthused about, is to see that, because I think that the study itself has significant merit, but I recognize there are limitations. So that's where my vote would be.

DR. WILLARD: Jim?

DR. EVANS: There's no question in my mind that such a study would be very interesting and give us important information. My biggest hesitation is not that. It's trying to balance that with the obvious incredible complexities of such a study, especially in the kind of environment we find ourselves in with the U.S. health system.

I think that perhaps to me the most interesting question remains can we get these kinds of data and can we derive most of the benefit of such a study through the types of case/control studies and the types of population studies, albeit more limited and focused, that are currently going on?

Talking about kind of doing the whole nine yards with really rich phenotypic data, with long prospective follow-up, I'm not sure that the information we get is going to necessarily be of orders of magnitude more value than what we can get from smaller studies, but we can certainly be assured that the complexity and cost will be very great.

So to me, the big question is not would this turn out important things? It would. It's could we get most of that information through the types of studies that are going on now and that are going on in other countries? That's the big question, and what we have to decide is would we recommend to do this with various recommendations around that or would we recommend a more limited type of focus. That's kind of my inchoate thoughts at this time, but I think we need to discuss it.

DR. WILLARD: Chira?

MS. CHEN: I'm not as negative about this. I think it's pretty innovative, and with the talk from Yvonne Lewis, I was very surprised about how engaged the public is willing to accept this, and if we could get the public involved and get that first step to recruit the people and let them understand this, we probably will be able to use that as a push to form policy issues, to have all the other stuff to put together to get this thing working.

So from that point of view, it is a very complex project and it's going to be a very expensive project, but with the help of the public, we probably will be able to work it out somehow.

DR. WILLARD: Kevin?

DR. FITZGERALD: I actually am reveling in the complexity and the challenge of this project because I think it in and of itself may be, and I'm trying to think of any other examples I could think of, but it may be right now the best opportunity we have because this is kind of new, so it's not politically entrenched. It's not gridlocked anywhere, though it may become that way once we get the public involved, so you have to ask Muin and Francis if they want to die in this trench.

(Laughter.)

DR. FITZGERALD: But here is a possibility of bringing something to the public that is right now not polarized or gridlocked, so that we could use this to get public engagement going and perhaps set a precedent, at least set a precedent, that way because this is in one sense no more complex or costly or anything than a lot of the other stuff that's coming down the pike that the U.S. public is going to have to face.

So if we can find a starting point -- and I don't know. I'm just trying to think

if there's a better one, but I like this one, not in the sense that I think it's necessarily going to work, but I think it's a great starting place for that kind of public engagement and discussion to see if it could.

DR. WILLARD: Agnes?

MS. MASNY: Well, I agree with everyone regarding the complexity of the project, but I fall back on what we were assigned to do in our charter is actually from the Secretary's Advisory Committee to actually look at the impact of the Human Genome Project on all the aspects of health, society, and medicine, and I think that if we don't support or fail to support a way that we could conduct this large population study, we will fail the charter that we were given to do.

So I think that from that perspective, that is one of the main reasons why we should move ahead in whatever fashion we take, whether we have to look further at some of the issues before we put recommendations forward. I think it is well worth and I enthusiastically support moving forward with recommending this to the Secretary.

You had asked also, Hunt, regarding some of the other key issues, and I think just to reiterate what people had said about the issue of community involvement and community engagement, one of the things that we would need to look at would be actually developing a whole new paradigm for the way research would be conducted with this aspect of community engagement. I know the CDC has a whole network of CDC Community Partnerships for Prevention, and we would have to look at both the national level of engagement of community partners as well as local levels, and maybe that would be one thing that we would need to look at a little further in terms of making our recommendations.

DR. WILLARD: Cindy?

MS. BERRY: In all of the comments that I heard today, I didn't hear that this was not a worthwhile endeavor. I heard that there are some complexities and there are timing issues and cost issues and things that we need to be mindful of.

So I'm in the category of the enthusiastic supporters for the concept. I mean, it's like going to the moon. I think others perhaps have used that example, and I see no reason why we can't think big and embrace the idea and regard our job as helping to guide the Secretary and helping guide the process so that we're on the right course. I think it's really more a matter of timing and making sure that things are lined up and everyone is thoughtful about it.

So I'm in the category of enthusiastic yeses and I think our report or our job should be in helping to figure out how we get there and over what period of time and addressing all of the different issues that were raised.

DR. WILLARD: Julio?

DR. LICINIO: From my own perspective, I see this potential study as both revolutionary and visionary, and I think it would give power that does not exist in current studies.

For example, I study depression, which, surprisingly enough, clinically relevant depression has a rate of 15 percent in the population. So if you study 500,000 people, you would have 75,000 people with depression who would be genotyped and that we know their phenotype and environment. That doesn't exist anywhere in the country. It would be a unique resource.

For obesity, the lowest rate I can think of is 30 percent. So that would be 150,000 people genotyped with obesity, and there is no way that (unclear word) is going to go

out and genotype and categorize 150,000 people with obesity.

So the difficulty I think is that given its unprecedented scope, we could talk about it forever and never get it done, so we have to decide when do we stop talking about it and begin it, which I think would be a key issue for the Secretary.

But then, on the other hand, we do not also want to kind of begin the project with built-in structural flaws that we're not voicing ahead of time. So a suggestion that I would make would be to define timelines for key elements and stick to it, and importantly I think give the Secretary kind of a suggestion that maybe we should decide what things need to be decided a priori and address those in a thoughtful way, but time-limited, and then go ahead and do it.

Then also, define other issues that could be decided as the project goes along, and then set milestones for those maybe, let's say, every year, and then set up new things -- you know, you don't predict everything that's going to happen before you do it -- and set deadlines for those.

But I think we should neither try to talk about it to death nor start without a thoughtful process. Those two things have to be very well balanced.

DR. WILLARD: Debra?

DR. LEONARD: Well, I'm in the yes camp. This is a complex project, but I think from the beginning we've decided that the U.S. has a unique population by the heterogeneity of it, we can't use other population cohorts, and we're behind other countries. We were a leader in the Human Genome Project, so it seems sort of sad that we're lagging behind other initiatives like this.

I do think we should emphasize that it will require broad government agency and private sector involvement and participation.

I think that there has to be a public engagement mandate starting at the beginning, now, as soon as possible, as feasible, and emphasize that while there are hurdles, the potential benefits for individual and public health are enormous with the additional potential for other non-health outcomes that are not the focus of this project, like happened with the space initiative. I think there will be other outcomes of interest in science among young people and other kinds of things that will come out of this initiative if the public truly is engaged.

Can I add one other comment? Which is I was struck by Dr. Duster's point about the taxonomy that's being chosen for the representativeness of the cohort, and I would ask to consider something like a zip code taxonomy or something. I know there are billions of zip codes, but it just seems that you're basing a lot on race/ethnicity, and I think there's a real danger in that, having heard what Dr. Duster said. I think that's overemphasized. If it truly is a gene/environment study, then you need an environment taxonomy of some sort that's not in this study currently. I mean, as the work group proposed it.

DR. WILLARD: And Sylvia?

MS. AU: Well, I think that I'm very enthusiastic about this project because the rewards will be probably be more than going to the moon.

I think that this also gives us an extremely great opportunity to show how research can be done right in a large population if we do it right from the beginning. Of course, as I said, I'm really supportive of the community participation from the beginning.

I think that we have to emphasize that this needs to be new funding. We don't have enough funding right now for the research that is being done. It's being cut all the time. We need to have new funding for this.

Finally, that the participants need protections, protections from discrimination, protection from not receiving the proper health care. I don't want the situation that Julio was saying about watching people get sick. That is not acceptable to me. So if you're going to participate in the project, those participants need to have health care.

DR. WILLARD: Great. That was certainly useful to me, I think. My sense is -- and I'm watching the clock, so whatever we do, we're going to do it in the next four minutes. I see Muin and Joseph, and then I'm going to try to offer some final comments.

Muin?

DR. KHOURY: I'm not supposed to give my level of enthusiasm to such a study because I'm the ex officio here, but I wanted to react to a couple of things, one of them what Jim said, because you're the only one who brought the idea of could we do it through some other means. I think it's very important to at least give advice to the Secretary as we move to implement this initiative -- and again, four people here on what I heard keep saying this is a study. I heard one, two, three, four. You know, it's not a study. It's sort of a big initiative, but it's very important to have what I call the knowledge integration piece, sort of what are we learning from the existing cohorts, what have we learned from the existing case/control studies, what are we learning from the biobanks that are moving forward, and then figure out a way to integrate that knowledge as we move forward.

I mean, this is not as trivial as some people think, because pooled analyses and meta-analyses are a very complex thing. When I presented to the committee I think a couple of meetings ago about what HuGENet is doing, the Human Genome Epidemiology Network, as a matter of fact, last week, we just had a meeting in the U.K., Cambridge, where we brought together 24 networks from around the world that are primarily disease-based. Half of them are cancer. Osteoporosis, heart disease, Parkinson's, et cetera. These are consortia that have already existed for the last anywhere from five to 20 years. NCI and others have kind of nurtured them, and from the European Union, and that have collected thousands of cases and controls on specific disease topics. They have pooled analyses and DNA and they're working together to integrate their knowledge about genetic variation and that specific disease. There are other cohort studies, like ERIC and Framingham and the Women's Health Study and the Nurses' Study and the Physicians' Study.

So I think it's very important, at least from my perspective, to put in the advice that as we embark on this new endeavor or new initiative, that we need to provide enough resources for that knowledge integration from all the existing studies, whether they're case/control cohorts or biobanks that are beginning to be launched. Otherwise, we may be sort of missing the boat here and we may be studying things that we don't need to study because some other people have solved that question. So knowledge integration is the key.

DR. WILLARD: And Joseph?

DR. TELFAIR: Mine is brief. Hunt, if you can just answer also your perspective as you asked us to, I'd be curious.

DR. WILLARD: And I thought I was going to follow Reed and reserve the right not to say anything.

(Laughter.)

DR. WILLARD: No, I'm very enthusiastic about this. I'm full of question marks, but I think everyone who has dreamt about this study is full of question marks on how exactly to proceed.

I think for me the two issues are public engagement and how you do that and how early do you do it, and then, two, how one might creatively look at the issue of smaller starting studies, because you can't start on day one saying we want 500,000 samples and we're off to the races. So where can one get information earlier from a smaller set to teach us how to do this project as we go along?

The Human Genome Sequencing Project did exactly that. That's why some of the model organisms were done. There was a learning curve, and I think I'd want to think about ways in which that could actually be built into the process, so that we could learn from our mistakes and avoid them the second time and see what some of the gaps are, which we can't even anticipate now.

But I'm quite enthusiastic about this, despite the levels of complexity and despite an awful lot of what ifs that would have to be addressed by the Secretary.

DR. EVANS: As the one person who is probably perceived as the biggest wet blanket --

(Laughter.)

DR. EVANS: -- my plea would be that we do exactly what Muin has suggested. We need to learn as much as possible from the kinds of studies that have gone on and are going on already so we don't reinvent the wheel and so that we do this right.

DR. WILLARD: So with that, my sense of the committee is that the committee at large would like the task force to work with Amanda and staff to begin to draft a report, draft an outline, which the task force can be iteratively examining, and we can pull in other expertise as we see fit based on what we heard today, and then hopefully bring that back to the full committee as a draft document.

It's hard to answer by when without turning this way to -- I think it's impossible to say by when until we actually begin.

MS. CARR: Well, it's helpful to have some sense of that.

DR. WILLARD: I don't see how this could happen before the March meeting, which is the next one, right?

MS. CARR: That was what I was wondering about. Not beyond that.

DR. WILLARD: No.

Is there a sense of the committee that that's a reasonable series of steps? Then it would come back to the committee in order to both vet the report and identify issues that need to be drilled down a little more completely in that.

Francis, you had a point or a question.

DR. COLLINS: Just I would like to know, would the committee in the meantime encourage further exploration of how to conduct the public engagement? Because it sounded as if that was pretty broadly endorsed and I would hate to lose the time between now and March to begin to try to put something more concrete together along that line if you all believe that that's critical.

DR. WILLARD: Are you asking for a sort of preliminary note to the Secretary along those lines?

DR. COLLINS: I don't know if you have to turn it into a note to the Secretary, but just a sense of the committee that would justify perhaps NIH spending some money on this and not feeling as if we're completely out there on the limb.

DR. WILLARD: I would think you have the sense of the committee that

this is a high-priority item that no one knows how to tackle and any efforts to learn more about how to tackle it would be welcomed.

With that, I would thank everyone for hanging through to the end. We'll reconvene tomorrow at 8:30 in the morning, and members of the committee planning to attend the dinner this evening, you should meet in the lobby at 6:40.

With that, thank you all.

(Whereupon, at 6:05 p.m., the meeting was recessed, to reconvene at 8:30 a.m. on Thursday, October 20, 2005.)