Overview of Large Population Studies Policy Issues and Possible Approaches
Huntington F. Willard, Ph.D.

DR. WILLARD: Thank you, Reed.

Good morning. Actually my being here is not just because I love this committee work, but Sarah is holding my passport and said I couldn't have it back until after this presentation.

(Laughter.)

DR. WILLARD: We actually have between now and lunchtime to go over not only the deliberations of the Large Population Studies Task Force, but the draft report which you have, in principle, seen and memorized, and to come up with a list of issues that we as a committee feel are important to the charge that was presented to us, and then identify some of the approaches that would be helpful in going forward. Those are the parts of the report that are left blank awaiting committee input today, and we'll need to be fairly deliberate to work through that between now and lunchtime.

So I will zip through my formal presentation as quickly as I can to give you some background of the task force's work to tee up many of the issues that the task force identified as a draft set of issues that the full committee can take on, and then we'll get into a general discussion.

So just as a reminder to those who actually were on the task force and also those who were not, this was the group that convened a number of times by telephone to go through many of the issues and to frame the report that you have in front of you.

The issue, just to remind everyone, not so much what the purpose of the large population study would be and then the resource that that study or studies would represent at the end of the day, was really the goals of those studies that has framed the task force's work and guided the shape of the document that you have in front of you.

What I want to do, both in my formal presentation and then to tee up our discussion session, is give you a bit of background and an update on some relevant events that are described in the task force draft report, focus most of our discussion on the various issues and potential approaches. And the charge to us today before lunch is to try to come up with a committee's view of what relevant approaches might be and potential recommendations that we can then shape going forward before we make those recommendations to the Secretary.

A little bit of background, to remind people where we've been. So we were requested by the NIH, now almost, heavens, three years ago, to begin to weigh in on the value of a large population study. This coincided with an important paper that Francis Collins wrote publicly making the case for such a study and the resource that it would represent. During our priority-setting process, as we heard just a few moments ago, this was categorized as one of the issues that required in-depth study, and then our task force was developed in October of '04 in order to begin work on this point.

A year ago, we had a full-day session presenting both different scientific approaches that have been taken or proposed to explore the kinds of relationships that a large population study would explore between genetic variation, the environment, and common disease, and as well, identified many of the scientific, social, ethical, and legal issues around such studies that we as a committee would need to weigh in on.

At last summer's meeting, we agreed to begin to develop a report to the Secretary that would identify those key policy issues, outline approaches that could be used, and then ultimately make recommendations about the types of mechanisms that would work best to address the issues that we identified.

Last fall, we had another day-long session with a number of in-depth presentations from scientists, ethicists, and from some public engagement experts to give us some insight into not only the key policy issues that exist around this issue, but also how to address them, and especially public engagement mechanisms and best practices in order to inform us of, again, the range of possible mechanisms that we can discuss later today.

The outcome of that meeting led to an identification of a number of those policy issues, gave us enough information to move forward to a drafting of the report, and importantly, as an overarching issue, reaffirmed this notion that the public must be involved at all stages of the development planning and the conduct of any kind of a study that would go forward. And it's that point which has guided much of our thinking on the task force and much of the drafting of the report that you have in front of you.

At the October '05 meeting, essentially a straw vote around the table was that despite the challenges of the study, there was clear, initial enthusiasm for the study concept because of its great potential. This was, I think, uniformly held, although the degree of enthusiasm or the degree of level and number of caveats that individual members of the committee expressed was quite variable I suspect. So that was despite the challenges.

But in addition, because of the challenges, we also recognized the need for in-depth analysis of the issues and the kinds of approaches that we need to be taking before any final decision might be made to go forward or not go forward with such a study in the United States.

So we aimed to develop at least the framework of a draft report in time for this meeting and that was put forward with the terrific assistance, first, of Amanda Sarata and then, in heroic fashion, Kathi Hanna, who stepped in to help us draft the report that you have in front of you.

Also at the October meeting, we were asked by the NIH for a sense of the committee -- and this is the point that Reed just alluded to -- on whether it should proceed with public engagement efforts. And as Reed just said, although in our advisory role, we can only recommend to the Secretary -- and that's the kind of recommendations that we'll discuss today -- but, nonetheless, we indicated that given the obvious importance to us of public engagement, we didn't wish to inhibit the NIH in moving forward, which I think was classic language that came from our chairman. And as you just heard, an RFA was, in fact, put out by NHGRI in order to take the first steps in that direction.

So there have been a number of other developments which are described in your booklets, and they'll be alluded to, I'm sure, during the discussion, and we can discuss them at greater or lesser extents, as people wish.

First was the Gene and Environment Initiative, GEI, announced by Secretary Leavitt as a key effort of HHS and the NIH.

The Genetic Association Information Network, another related study, as a partnership between the NIH and the private sector.

Further progress on the National Children's Study.

The RFA from NHGRI that I just alluded to.

And then the announcement by the VA that it was going to form an advisory committee on genomic medicine to guide its efforts for the program that it is hoping to mount in this direction.

So there's plenty of activity that's going on around us and that our work can, hopefully, inform and we can, again, reflect off of these to guide some of our deliberations this morning.

So we, being the task force, were charged at that October meeting to draft a report. There were three steps to this charge.

First, to delineate policy issues and the questions that policymakers would need to address. And the first attempt at that is contained in the draft report in front of you.

Two, to explore the ways in which these questions might be addressed, including any variety of smaller, intermediate research studies, pilot projects, or policy analysis efforts that will be needed, and that's very definitely what we're to talk about today.

And then thirdly, to determine in the committee's opinion which approaches are optimal and, therefore, would form the basis for recommendations to the Secretary, and that's also on the docket for discussion today.

So the scientific background of the report, which you've all read, is shown here, describing briefly the kinds of methods that would be used and are being used to identify the genetic basis of disease, especially common diseases; providing some background, which you've also heard several times in the life of this committee at these meetings, of various biobanks around the world in large population studies around the world; and then an overview of a hypothetical large population cohort study mounted in this country, as outlined initially in that paper by Francis Collins and subsequently addressed also by an expert task force or working group, whatever the official name was, that NHGRI pulled together to examine some of the scientific issues.

So there are really six key points that the task force identified, and that provides the framework for the report that you have in front of you. There's an overarching issue, which is this need for public engagement, and that we addressed by itself in the draft report, but it also provides relevant points underneath each of the other five issues which have around them a series of questions and issues that the committee will have to finalize today, those five policy areas being research policy considerations, research logistics, regulatory and ethical considerations, public health implications, and then finally, social implications. And in all of those, to repeat, we would anticipate the need for public engagement in order to best inform those as we go forward.

So, first, why public engagement matters. What this is is a screen shot of a brief editorial that came out in Nature in the March 16th issue with the headline that says, "Huge Biobank Project Launches Despite Critics."

The notion there was that the U.K. Biobank is actually getting off the ground and beginning to collect samples from their ultimately hoped-for half a million participants. But there are still critics some many years after they have engaged in a series of public engagement efforts. We heard from representatives of the U.K. Biobank at at least one, if not two, of our meetings. So they've actually provided a model for how we might go forward, accepting and acknowledging

the sort of cultural differences both in science and the society at large between the U.K. and the United States.

Nonetheless, having done that in a diligent and open fashion for several years, they still have a large number of critics who are saying that the project isn't ready or shouldn't be taken up or who are concerned about the kinds of information that would come from it. And one of the issues is that -- and there's a quote that is shown on that -- the "complaints stem in part from a misunderstanding of the scheme." So even several years down the line with that study, and the cohort study and the resources it would represent, being outlined and aired in public again and again and again, there still is an acknowledgement that there's a misunderstanding of what they're trying to do and what the purpose of the Biobank would be as they set out to do it.

So I think this provides to us a bit of realism of the challenge in front of us of exactly why a public engagement in this public engagement in this country will matter as we go forward.

So here, just highlighting some of the points that are also made in the document, why public engagement matters. It's expensive. The public always pay attention when there are expensive projects of this magnitude. The scale of the study dealing with a half million to a million Americans is enormous and enough to get public attention, and those are not only people who potentially might want to be enrolled but also people who in their viewpoint especially would be exposed to the potential risks, as well as the potential benefits, of course, of the study as it goes forward.

It's a long study, which means it will capture people's attention and immediate results will not be forthcoming. By definition, this is going to take substantial time before potential benefits will accrue.

And then because of the potential significance and social implications of the large population study, public engagement will be necessary again at every step.

So one of the key questions that the task force identified in the draft report is at what level does one engage the public. Is it at a go/no go decision point, whenever that decision point might be? Is it at the level of the study design and planning? Is it at the point at which the study actually initiates in which you try to bring the public along at that point, or is it throughout all phases of the study from the very beginning, all the way through to the very end? Those are questions that the committee can choose to endorse or debate, and hopefully, we'll get to that later this morning.

Another question is, what do we actually mean by the public? Engaging the public means different things to different people. Are we talking about the lay public, the individuals whose samples might be or who might actually participate in this large study? Are we dealing with the scientific public? Are we dealing with our elected officials both at the federal, state, and local levels who would be dealing with this at some level, or again, all of the above? And perhaps the mechanisms and the approaches that one might take to engage any of these three groups might, in fact, be substantially different.

When does one engage the public? Right away? Later, when a decision about the study is made, again either go or no go? Or is it after study design and planning have been completed so that there is actually the details of a study laid out in front of the public? What questions might be the public be asked for their input, or is it all matters that one might ask for their input? And again, which subgroups of the public need to be engaged?

So those are the overarching issues that I think we need to keep in mind in trying to guide or shepherd some of the discussion for the rest of this morning. I'll continually come back to this point I think.

So then there are five key policy topics, and I've arranged my slides here in this manner, identifying each of those and going through the various considerations and the questions that the task force identified, which the committee, again, is invited to either agree, disagree, add, or subtract as we go forward this morning.

The research policy considerations that are relevant are questions like what is the need for such a study. What is its value and cost? What would the effects of funding this program be on other areas of research priority in this country, and can existing studies either in this country or elsewhere achieve many or all of the same goals? These are not scientific questions, but these are science policy questions that the task force felt were important for advising the Secretary.

Additional questions. Should there be collaboration with other countries, as I just alluded to? Which agencies in HHS should be involved? Which agencies should take the lead in such a project if one is going to be mounted? What should be the role of the private sector? And here I think this is where the GAIN project, which has been announced as a partnership with the private sector, is both exciting and very relevant to our deliberations this morning. And what intellectual property policies might govern the study as a matter of research policy?

And lastly, given that the long-term cost required to mount such a study would be significant, if not unprecedented -- and there clearly is a lot of uncertainty about the ultimate costs of such a study -- would it be possible to sustain support at all the levels, public, scientific, and elected officials, for such an investment over such a long period of time?

So those are the questions the task force identified, and there are a number of issues relevant to those research policy considerations that are outlined in the report, and the report is organized exactly in this manner to remind you of what, hopefully, you've already read through.

And continuing, so not only the need for and the potential benefits of the project, but its costs and effects on other areas of science priorities in this country, the current capacity to conduct such interdisciplinary science, the potential need for various partnerships, and intellectual property concerns and access. And each of those issues is flagged in the report.

Policy topic number two related less so to the policy issues and more so to the logistics of such a study. How will representativeness be defined and achieved in terms of who are the 500,000 to 1 million potential participants.

Given that the study's benefits to individual participants may be only indirect, would it be difficult to recruit a broad range of study participants? And the experience in other countries is probably relevant in this regard.

What are the ramifications of using racial or ethnic categories for codifying different participants? That's an issue which I think the task force felt quite strongly that there were a number of issues there that would have to be examined before going forward.

And then will the underinsured or underserved be part of the study, and if so, how does one ensure that they're recruited in sufficient numbers?

Under research logistics again, how will the non-genetic study variables be defined and studied in the realm of the large umbrella called environment?

Given that this is going to need to be decentralized to several different sites around the country, if not many different sites around the country, would the lack of uniform methods that define our health care system in this country make a study of this scale either difficult or impossible to implement?

And will new technologies be required especially to collect environmental data? Within the NIH NIEHS is substantially ahead on this issue in defining exactly the kinds of new data that will need to be collected and the new technology developments that will have to be in place.

The issues that are flagged in the report around research logistics involve enrollment criteria and recruitment of racially or ethnically defined groups measuring various differences in the population across many different sites, coordination across multiple institutions and health care systems in this country. The committee again will have to weigh in on those particular issues.

You'll notice, just if I can take pause here, what I'm outlining are the questions and the issues. The task force has not outlined, although we have some ideas and some thoughts on this, the various approaches that would be used or could be used in order to address those questions and issues. Again, that's what the full committee needs to be thinking through in order to guide our discussions later.

Key policy topic three on regulatory and ethical considerations. The questions here of regulatory requirements and how they might be met, how informed consent would be carried out and obtained, and whether there are unique considerations for a long-term study of this magnitude. Would the study provide health care to uninsured participants, and if so, how would that work? And are there special protections for children or adolescents who might be enrolled in such a study?

Who will have access to study data and under what circumstances and how? Does that, therefore, require special arrangements to enable the participants to have some measure of control over how their individual samples or the data that would be obtained would be used and by whom?

And would the study be able to accommodate participants' expectations regarding the confidentiality of their data? This goes, obviously, to the much larger issue of privacy of genetic but even also environmental data, which we've tackled on several occasions previously.

Will additional privacy protections be necessary and for how long, and how would the research data and samples be stored?

And would the study results be returned to participants and under what set of criteria?

Again, many of these questions are addressed in many different settings, many different projects, large and small, but because of the large-scale nature of this particular project, the task force felt that it heightens the awareness of these issues and therefore their importance.

What Federal laws and regulations would be needed to be considered in deciding whether to return or not results to participants and their family members, and then how does one deal with the issue of family members who may not themselves be participating in the study, but who

clearly would be interested in the information because it would be relevant to their own health situation?

The issues flagged as a result of those kinds of questions dealing with IRB review, informed consent, whether, in fact, it is possible to have informed consent, given the lack of public understanding about a study of this nature and the level of prospective thought that needs to be in place.

Issues related to providing care and what the report refers to as the therapeutic misconception about what can or cannot be done when the data are available, privacy and confidentiality issues, control of samples and data issues, and then the larger issue of returning research results or not.

Topic number four, more in the public health realm and the implications of that. Will the statistical genetic associations be robust enough to lead to new therapeutic or preventive strategies?

Will such a study widen the gap between what can be diagnosed and what can be done about it, which is a standing problem in many such studies but may be particularly acute in a study that's this large and this publicly discussed?

And will all the data from the broad population be applicable to individual communities and groups who are defined by a variety of different cultural, genetic, and ethnic means?

How will the study results be implemented by regulatory health and safety agencies at different levels around the country, given the complexity of population risk assessments and the balance between population risk and individual risk assessments?

And do the regulatory agencies, public health departments, and health care providers have sufficient resources in order to translate the knowledge that such a study will generate? This, obviously, is a longer-term issue, but there's a need for those health care providers and regulatory agencies to be ready to act on the data as they become available.

Last on the list, but not last in importance, of course, the notion of the social implications relevant to a large population study of this magnitude. Could such a study create or change the way that we currently think about health disparities? Will the findings exacerbate existing vulnerabilities, such as age, race, and disability? And if the study leads to the identification of new vulnerable populations, will there be sufficient public health or social resources available to respond to such new vulnerabilities?

If the study generates clinically useful information, will it benefit only those who currently have access to the health care system and how does one ensure that, in fact, all citizens in this country would benefit from those findings?

Can or how would the study results be realized in what is currently a significantly decentralized and fragmented health care system? This is clearly one of the differences between a U.S. study of this type and similar studies mounted in other countries that have different health care systems.

And would the findings from such a study exacerbate racial discrimination or other types of discrimination and group stigmatization?

What are the views of minority communities about the study's implications?

Will the study pose or increase risks of genetic discrimination?

And will the study findings lead to very reductionist explanations of the role of genetics in disease, which has been a challenge for the genetics community for some time?

The issues that are flagged in the report to address those questions relate to elucidating and/or exacerbating health disparities, the risks of genetic determinism, developing reasonable social and policy responses to anticipated research findings. And all of those questions fit largely under those three particular bullet points.

So our goal today is to review and discuss the policy issues that I just ran through, and hopefully that you have read at leisure in your looking at the report, go through those for completeness and relevance and less so wording. This is not a wordsmithing session. We're nowhere at that point, but we do want to have a fairly complete list of the issues that the committee at large feels are relevant to the policy issues that I've just outlined, and determine whether they should be prioritized. In what I just spelled out, there was no effort at prioritization. It may be that some of the issues are considered to be a substantially higher priority than others, and if so, do we want prioritize them within the report?

And then most importantly, we wanted to discuss approaches today for addressing those policy issues and developing additional options, which would lead us then to a series of mechanisms that we might recommend to the Secretary which was, in particular, the charge passed down to us by NIH Director Zerhouni.

So in kicking this off, I want to come back to the larger broad issue of public engagement mechanisms, mostly to point out exactly how large and complex these issues are, at least in the eyes of the task force and use that as a point of departure for moving into a broader discussion of all of the issues that we've identified.

So when one thinks about public engagement mechanisms, there are a series of different mechanisms that one might contemplate, depending on which issues the public is being asked to address. So if they're being engaged around the actual initial conceptual question of should there be a large population study of this type, then as we heard in some of the presentations last meeting, there is a range of different approaches from surveys carried out nationally or locally, state referendums, trying to work with Congress directly to look for their support or funding in their role as the elected officials representing the public, town meetings around the country, focus groups, and on-line collaborations in order to provide Web-based materials for the public. And to greater or lesser extents, each and all of these have been used in other countries where the mechanism is relevant to obtain support for the programs that have already been outlined in those countries.

If, at a different level, the question is to engage the public around operational questions concerning design, planning, conduct, follow-up, and reporting of the issue -- and this isn't to argue that the public is going to tell the scientists what to do, but it is to say that the public may have a role in order to, at some level of sort of a 5,000-foot view, comment on the kinds of questions and aspects of the design of the project that they might find relevant, again possibly town meetings, focus groups, or Web-based collaborations.

A group of us took an initial stab at some of the issues just to frame again how complicated and how complex issues of public consultation may be. From the original conceptualization of such a study, outlined at least first publicly in the paper that Francis Collins wrote that I've already

alluded to, the NIH pulled together a design considerations work group in 2005, and we entered the fray also in 2005, but now in 2006.

Around the issue of public consultation, there's actually consultation at a number of different levels and with different people. We've identified all of this, in principle, would happen before one would move into the pilot stage, whatever the pilot stage for the ultimate project is, whether it's this detail or some other detail, and then kicking off the actual project, the kicking-off stage being where the U.K. Biobank is now, having started back here at least three, if not four, years ago and maybe even longer. Francis, I'm looking to you. For the U.K. Biobank four years ago. So this for the Biobank was a four-year process before getting to kick-off.

But to make it a little more complicated, at the consultation stage there's actually a large number of different groups that can be analyzed in public consultation. There are issues around protocol development that would have to be tackled. There are very substantial issues around education and training not just of the public, meaning the research participants, but also the physicians and scientists who would be involved and policy experts at different levels around the country that would be interfacing with this project as it would go forward, and then very substantial issues around database development, privacy, who would have access to that database, what structure would it be, et cetera.

Ideally this would be an iterative loop among all of those, as I've attempted to outline here, because in the general public at large, one might contemplate surveys or focus groups, town meetings, as we mentioned, and a broad-based educational campaign, perhaps similar but inevitably on a larger scale than what happened in the U.K.

There are also disease advocacy groups around. I've listed three here, but there's a whole host of advocacy groups around the major common diseases that would likely be encountered during the lifetime of such a study. And these are groups which are important not only because they've given substantial thought to the specific issues that they would be interested in as representatives of the public around their particular disease, but also because having them on board, if there's a decision to go forward, will greatly assist issues of general public engagement through arrows that are not on this slide but which would tie these two together.

And then public consultation of the scientific and professional organizations both to address scientific merit, which is not our particular remit, but might be a remit of other groups, but also at the level of the National Academies or the Institute of Medicine and other groups involved that have both experience and would be needed to assist on issues of either recruitment or data collection or study design.

So there are really three very different levels of public consultation which would have to, at some level, go on separately but then somehow interdigitate with each other in order to develop some kind of matrix of public engagement information that would be relevant to then feeding back on a project. This wouldn't go on simply as an ancillary activity, hopefully to "talk the public into this" as a good idea, but that this actually would feed back on the larger design where one would need to be prepared to act on the feedback and, if necessary, revise the study goals or design and go back in an iterative manner through multiple rounds of consultation, all of which might ultimately then precede a go/no go decision either at the level of HHS or the Congress or the various groups that would be called to do that.

So I outlined that simply to illustrate the magnitude of the challenge that I think our committee has before us not to have the final word on any of these issues, but to identify what the issues are,

raise the questions, and really anticipate what we think some of the most successful mechanisms might be to deal both with the public consultation issues, but also the five key policy issues that I outlined previously.

So I think at this point, what I would like to do is open this up to initial discussion and response and information-gathering among members of the committee, including the ex officios. Then once everyone has had a chance to weigh in on what the task force has done, move into a much more deliberate analysis going through each of the key policy areas that we identified in order to take a look at the questions, take a look at the issues, decide what we want to do with those, and then go to potential approaches and mechanisms. That will then help the task force after this meeting as we go back to continue our work and help Kathi with continuing to draft the report, ultimately getting to a point at several meetings from now where we would come back to finalize the report from the full committee.

So, Mr. Chairman, I will stop at that point.