**Roundtable Discussion with Session Participants**
***Facilitator: Huntington Willard, Ph.D.***

DR. TUCKSON: Well, here is what we're going to do. We have got such a rich panel and we have so much to do, we're going to go 10 minutes into the lunch section, even though we still have that other work that we've got to do. This is going to get very interesting. I don't want to shortchange this panel. We can't do that. So we're going to go 10 minutes over 1:00 to 1:10. We're going to give this a very good listen.

Again, on behalf of the entire committee, thank you to all of you who have presented today.

With that, Hunt, let me turn it over to you to moderate.

DR. WILLARD: Thank you, Reed.

Let me add my thanks to the speakers, especially for keeping to time, which will keep us on task. I want to thank the members of the task force that put this session together. Although she just walked out the door, I want to specifically thank Amanda for her diligence and hard work in getting this day scheduled.

We do have about a half hour, and I want to divide that first into sort of a question and answer session, because I'm sure that members of the committee have questions that we've been storing up as we've gone along, and then touch on a few general issues.

I'd also like to remind, especially the committee, that although all of this is fascinating and we have dozens of questions that we would just like to fill our brains with answers on, the reason for having this session today was for us to decide whether we had at hand all the information we needed, or whether there were in fact gaps in knowledge and a basis upon which to make a recommendation or recommendations to the Secretary regarding large population cohort studies.

So let's keep that in the back of our mind. When we're all done, in addition to taking a lot of information home, we need to address that question of whether in fact we're going to continue any further with this study. So with that, let me open it up to questions.

Ed, I have you first.

DR. McCABE: Yes, I think I see one of the major barriers being IRBs. Having gone through the California pilot tandem mass spec project where every hospital had to get approval through its IRB, it shut down that project as a global project for the state.

So I have it for Dr. Brenner and also Dr. Guttmacher. Both of you have dealt with this in your presentations, but I see this as a huge barrier to
multi-center studies. So I was interested, especially when you're dealing with community hospitals, how can you deal with the IRB there?

And then Alan, you had a very pie in the sky approach that many of us have talked about about getting rid of the I of IRB so that we can do multi-institutional collaborative studies. But I'd like to ask the two of you how you plan to actually turn this thing around.

DR. GUTTMACHER: Well, we're luckily at the much earlier stage, so I don't have to claim that we actually have a plan for turning it around, but we can see a way that we might get there. But before I even answer your question, as long as I've got the microphone, let me take exception to my own presentation by pointing out that since I gave the presentation some many minutes ago, I have learned that due to technical problems, the report that I promised would be up by close of business today will still be up by close of business today, but close of business today may not be until the end of this week.

(Laughter.)

DR. GUTTMACHER: So in the next week or so, possibly even the beginning of next week, but we think we should have it solved by the end of this week. It may take a couple of days to get it up there.

In terms of central IRB, this was not completely pie in the sky, but obviously some of that. That is, to really think about a study of this scope in lots of ways to work, we thought it really would require a more centralized IRB mechanism, than is common today anyway. That might not mean one that is completely centralized. In other words, it might well be something where the local institutions still had some plan, because clearly the local communities and populations involved need to have a role in this.

So how one then does that but still has a centralized process to streamline what would happen at the local institutions. Again, in this report there will be a little more detail about this, but it is not that we have a concrete plan about exactly how it is going to happen.

On the other hand, as I'm sure you're aware, this is a sort of movement that is afoot in biomedical research in general, largely borne out of the frustration that not just researchers have felt, but also institutions have felt as research has gotten both more multi-center and more complex to deal with the issues.

Those in the genomics and genetics community have certainly seen where we went before IRBs ten years ago. The universal response of course was from the IRB genetics, we don't know anything about it, so go ahead. Then the universal response became genetics, we know nothing about it, so you can't do anything.

So there has been a realization of that. But a lot of other non-genetics communities have looked at the question of centralizing this. There are beginning to be some examples of doing it. So we're optimistic it can be done, but do realize it would be a challenge. It is not to say that local institutions would have no review or oversight at all.

DR. WILLARD: Dr. Brenner, anything to add?

DR. BRENNER: Well, I would just echo the comments that were just made. We also are hoping that we'll be able to get a more centralized process, but we have the vanguard phase in place to look at that with the first set of small scale where there are a few number of centers, and then expanding to additional centers. We do have somebody, Alan Fleischman, in our office, who is looking specifically at these issues and challenges.

DR. McCABE: Well, I would just like to register this as something that we highlight as a barrier for these sorts of studies if we proceed with the report.

DR. WILLARD: Yes. Well, after lunch, we will come back to a committee discussion of this, and we can pursue it then.

Kevin, I have you, and then Emily.

DR. FITZGERALD: Thank you. I have a somewhat more global question, so I throw it out globally to the entire panel.

In a lot of the different presentations, and let me first preface that by saying this is following up on what Dr. Rotimi brought up about the complexity of groups and how we try to group people and how sometimes that's not an accurate way of truly understanding the situation.

Many times in the presentations, people mentioned things like the public responds well to this, or we're looking for public transparency, or we have altruistic participants for these projects.

If you take that and then put that together with the idea that I also heard I think several times of harmonizing these different databases, or these different projects, what I'm wondering is do we know, or will there be harmonization of the understanding that these participants will have as to the real risks and benefits they see to these projects. Lest we assume that we as experts represent what they perceive to be or understand the risks and benefits of this type of pursuit of these types of projects, databases, and that sort of thing.

I would imagine that within any nation, even with the U.K., there is incredible complexity. You would have all kinds of subpopulations and subgroups breaking out and seeing these identical projects and identical processes in very, very different ways with different expectations, different motivations, different reasons, perhaps initially coming to the same conclusion.

So in this process of harmonization, what input do they have? Certainly about risks and benefits, but also as things go along, can they affect change? Can they guide the process? Are they going to have them put into how the harmonization is done? I know that's a big question, but it is one that is coming up I know more and more in the social science literature, and I think we need that to help inform us of the best way to go forward. So I kind of throw that open to anybody who might have a response.

DR. MANOLIO: Obviously it's a complex issue, and it gets at the heart of community-based participatory research. It's a shame that Gil is no longer here to be able to address it.

I think that all we can do is the best we can do, and try our very best to have ongoing and active community consultation and involvement from the get go on these studies. I think many of them, and John and others will talk about how they have done that in their existing studies, all you can do is listen and try to adapt and modify as you go along.

DR. NEWTON: I think that's right. I think perhaps one thing to say is there are different levels at which you could consider the public. You've got the public as represented in the studies, so you have to make absolutely sure that the risks to them are minimized, and that they understand their relationship with the study.

But then there is also the broader public. It wouldn't be right for the public in the study to necessarily speak on behalf of the broader public, the target public. It is notorious.

I was picked up by a member of Parliament. I said, slightly glibly, "We'll maintain a dialogue with the participants. He said, "How are you going to maintain a dialogue with 500,000 people, Dr. Newton?"
Of course, the answer is you can't. To some extent, of course, his point was that we are the elected representatives of the public. Therefore, perhaps we should have a role.

So I think you have to think of the public as the public themselves. You can have direct access to them, you can have the institutions that speak on behalf of the public, of which there are a number, and there will be U.S. equivalents. We have the Human Genetics Commission, we have Parliamentarians, and we have House of Lords.

So you just have to, as Teri says, do the best you can, and listen.

DR. ROTIMI: I'd like to add to that. I think part of having a dialogue with the community is making sure that the people that have the community interests are actually present during your design phase.

I think one of the things that happened in all of this, it is very difficult. We design studies and we take them to communities. We say we are engaging the community. That is very, very difficult to do, because in a sense, when the community really challenges us with difficult issues, we really don't change our strategy. We just find ways around it.

So are we really engaging communities? Or are we just doing these things to make sure that we get the necessary approval, or that we do what we want to do anyway? I think those are issues that we have to really confront in all of this. I have to say that they are very difficult. Sometimes we really don't want to hear what the community has to say about what we do.

DR. DESCHÊNES: If I may just add, I talked a lot about organization of the legislation and ethics. I think the aim is certainly not to have one legislation that fits all. That is certainly not is what is going to be respectful of what participants and communities want.

But we need to be able to discuss and to have a dialogue where people will understand each other. For this, we need to talk to our community first, and then go and try to exchange with other biobanks and biobankers.

DR. WILLARD: Thank you.

Emily, I have you next.

DR. WINN-DEEN: My question is directed to Dr. Brenner, but it may be to the whole U.S. team as well.

In your presentation, you were the only one who mentioned that there actually was an act of Congress required to fund your study. I am curious whether you think that will be required for other large studies in the U.S., or if this is sort of an anomaly that has to do with, because it was kids, or really what the genesis of that being funded by that mechanism was, and whether it is going to apply more broadly to other population studies in the U.S.

DR. BRENNER: Well, I guess I can talk most specifically about the National Children's Study. What I was referring to was the Children's Health Act which authorized the study, but it didn't appropriate the funds. So there is a difference between authorizing it and appropriating the funds.

In terms of whether future studies are going to require specific authorization, probably Dr. Guttmacher could say.
DR. GUTTMACHER: Yes. I won't make you, Ruth, responsible for funding our study.

I think the kind of thing that we're talking about, it is clear we were talking about the science of it, not the funding, which would be a huge hurdle. The only way to imagine something like we're describing going forward I think is to think of not just innovative techniques for doing the science, but innovative techniques for doing the funding.

Those would include, for instance, thinking about this as a public/private partnership. Now, that's not the first time that has been done. It's not even the first time it has been done in genetics, obviously. But the kind of funding that something like this would need, I think one would need to really look at bringing in non-governmental payers, the kind of data we think would provide and would again be freely accessible to anyone with IRB approval, which would include commercial entities that had IRB approval.

We think it would be salient enough and one could make enough of a case for it to interest private payers. We have had conversations with folks who have heard something about this in the private sector who have said gee, this is actually something that nobody has signed any checks because there is nothing to sign any checks for. But this is the kind of thing that in fact if it was done well, we could actually see getting involved in.

Now, of course that is not an unabated pleasure. If that happens, it raises obvious concerns on the parts of various participants, one could project, about well gee, if this is being funded by industry partly, what does that say about it? So one would need to be very thoughtful and have lots of people involved in that kind of conversation.

But I think this kind of thing, if it were ever to see the light of day, it would require some innovative looks at funding.

DR. TUCKSON: Ruth, just to make sure, did you say that your study, the Children's Study, is not actually funded?

DR. BRENNER: It's authorized.

DR. TUCKSON: But there are not dollars in the bank?

DR. BRENNER: After authorization comes appropriation. It is not appropriated, it is authorized.

DR. TUCKSON: So you don't have the money?

DR. BRENNER: We have currently in existing agency budgets funding for initiation of a study. But to stay on the current timeline, we would need additional funding in '06.

DR. WILLARD: Barbara, I had you next.

DR. WINN-DEEN: Can I just ask a follow-up? It is not clear to me. Was this the outlier? Is there any other study that we know of in the U.S. that went through that process of some kind of congressional act, even for authorization? Or was this an exception?

DR. MANOLIO: The Women's Health Initiative was funded that way. I don't know the exact technicalities of whether it was a law, an act, or whatever, but it was funded by a congressionally mandated line in the NIH budget. The Genome Project may have been the same.
DR. WILLARD: Barbara?

MS. HARRISON: I had two questions about recruitment into these large population studies. I'm directing the first one to Dr. Rotimi, as well as Dr. Guttmacher, and the second one to Dr. Guttmacher.

The first question has to do directly with Dr. Rotimi's talk. Of course, in the literature there is a lot of information out there about how race is not an appropriate proxy to use where we are trying to make sure that we get these diverse samples.

So I wanted to hear a little bit about your thoughts. If we think about doing a large population study in the United States, what are your feelings about what could we use? I mean, is it still appropriate to use race in the sense of making sure that you get sample populations from several different parts within the United States? Or is that just something we need to completely throw out the door and bring in something new? If so, what are your ideas on that? I don't know if that was the topic of conversation at all at this meeting.

Then again, also around this topic of recruitment. It seems that for many of these large population studies, the medical institution is the place where people get recruited into these types of studies. We know that there are many people in the United States that do not use medical institutions for their health care. They don't have access to it, or they don't have insurance.

So again, in the conversations, I was just wondering if that was something that came up, and was there some kind of way to address that?

DR. ROTIMI: Yes, I think the issue of whether to use race or not is something that we've talked about multiple times. There are really multiple ways to answer that question.

I think at a philosophical level, if you say the word is race, I have to go back to what my zoology teacher defined, and that is subspeciation. We don't have that in terms of human beings, but it is a concept we have used to describe ourselves.

When you talk to the average person in the street, they will tell you that they know what race is. But when you really go down to the detail of trying to say what about Tiger Woods, what is his race, then you start to see the level of confusion. But at the surface, people will sort of say, I know what that is. I know who you are, I know who you are.

So in terms of designing studies, it really does come down to what is it that you are trying to do? What are you trying to answer?

For example, I gave the example of eating beef earlier. It is a very good example for me, because I like to take things at a very simple level. If you want to study how people eat beef, then you need to incorporate that into your study, or you won't be able to answer the question.

If you want to see why African Americans have twice the rate of Type 2 diabetes, then you need to look at what are the things that African Americans do, for example, that whites don't do in this country that puts them at a higher risk. You need to look at the type of drug they get.

So I think it is really what we do is we use proxies to define things that we really want to get at. Sometimes we want to get at income. We look at it in terms of African Americans, because African Americans tend to be poorer than whites.
So it really does come down to what is it that we are trying to answer? How do we design our studies in a way to make sure that we have under that umbrella the things that we want to measure?

For me, I look at ethnicity as a good way of people identifying themselves. What ethnicity does, it creates the flexibility for people to move between groups. I'll give you an example.

In Nigeria, for example, where I grew up, because of the way people get married and the custom, if a Yoruba marries an Ebo and the woman happens to be Ebo, the child is Yoruba. So the child grows up as Yoruba. If that person comes to the United States and says, I'm Yoruba, they have Ebo also in there.

So it really has to come to our level of understanding and appreciation for some of these things. Also to acknowledge right away that it is not the best, and to identify the errors or limitations associated with our designs.

DR. GUTTMACHER: Let me handle your second question first, because that's easier for me. That's the question about the medical center and the bias that it would introduce.

That's one of the several reasons why we really saw the household unit as the recruitment unit, to get away from that very bias that that would obviously contribute. The whole issue of race/ethnicity you'll see was one of the six descriptors that we thought should be used. Ideally we would think that such a study should reflect the population of the United States, which means ideally it should be a 290 million person study.

That probably would be very difficult to find a budget for. So what are the key things that one needs to include if you're looking at genes, environment, and health, and what are those other descriptors of individuals that make a difference? Well, age does, gender does in our society, and for similar reasons, race and ethnicity do have something to do with one's health status. Now, many of us suspect not much of that has to do with genetics, but since this is about genes and environment, to be inclusive of that, we thought we needed to include groups.

Now, the problem has become how does one identify racial and ethnic groups in the U.S. We know we do it poorly, but how is it done? Well, there are social definitions that are widely used in other kinds of research. This was a lengthy conversation, I should add. But the feeling was with all the limitations of that, since they are so widely accepted and used, that it makes sense in terms of inclusion of making sure we include and use those to make sure we're reflecting the spectrum of American society.

DR. GOLDSTEIN: Let me just add something to that. We have to expect at the outset that there are going to be differences in the specific gene by environment interactions that occur in different racial and ethnic groups.

So if you want your study to inform about all the different racial and ethnic groups, then you really have no choice but to consider that in the sampling design. I think that that is clear. But it goes farther than that. It is insufficient just to simply say we want to include this number of each of the racial and ethnic groups.

For example, we know that individuals that identify as having European ancestry in America are more genetically homogeneous than individuals that self-identify as either being African American or Hispanic. So what that means is if you just say yes, we're going to get a certain number of individuals that identify as European American, you might do a pretty decent job of representing the genetic variation in that community, and therefore do a decent job of looking for gene by environment interactions.

But you might end up with a very biased sample of Hispanics, because you haven't actually done a good job of finding out what is there and figuring out a way to make sure you represent what's there.

So you have to think about exactly for each group how to represent it. And then going a step further than that, you have to think really hard about the representation in the study. If you just go by the proportionate makeup of the U.S., then it is true, it is just a fact mathematically that you will have more power to identify gene by environment interactions in those groups that make up a larger proportion of the U.S. population. You have to decide whether or not that's acceptable.

DR. WILLARD: Thank you for that.

Reed, I have you next.

DR. TUCKSON: I guess for the folks from the U.S. government agencies, given how extraordinarily expensive and how complex this stuff is, I didn't get the sense, and I'm not sure that there is an interrelationship, a functional coordination of the three activities that we heard about.

We've got an NIH activity, we've got CDC, and we've got NICHD. Given that nobody really has the money it sounds like yet, I mean, we've got all kinds of promises, but nobody has got any real hard money. Are we still talking about three different activities? Or are we talking about a Secretary of Health who has sat down with these three agencies and said look, folks, this is the way it's going to work.

Or is there at least in the absence of that, somebody going to the Secretary of Health and saying, we've got three different activities that are going to be coordinated in the following way to make the maximum use of the resources that maybe, with a prayer, will actually ever get funded. What's the answer to that?

DR. GUTTMACHER: We've had extensive conversations, all three groups together. They are ongoing consultations amongst the three of us to look at ways clearly that they would interrelate. Particularly we have had numerous ones with the National Children's Study thinking about the ways that recruitment might be shared, and the other kinds of ways that one might both for logistic reasons and also for scientific ones, the ways one might coordinate.

Clearly there are differences about what they want to achieve, but they really are complimentary. All three of these. I don't think that any of us have been thoughtful about this and would say gee, of the three, this is the most important, this is the second. These are all things that we think those of us who care about health, genes, and environment, all three of these approaches we think have not just validity, but importance. They help complement each other. There is some overlap between them, but the idea is really to minimize the overlap and use the opportunity to really make them complementary to advance each other.

So I'm not saying it would be wrong to have somebody from above do this, but we really believe we are doing it already.

DR. KHOURY: My message is the same as Alan's. I guess what we're doing at CDC is not to replace the AGES study, but something that needs to be done anyway, whether that is an AGES study or not, which is sort of this global collaboration.

If there are resources in the federal government, we'll all line up and work together. We are working together. I mean, NIH is part of the HuGE Network. We have been part of the discussions. The NCS is three or four agencies coming together.

DR. TUCKSON: Have you all put together any document for the Secretary's review that allows the Secretary to see how the pieces come together?

DR. GUTTMACHER: No. We've had various discussions of documents for other people, but we have not had anything. Again, we don't have a document for the Secretary about AGES, because again, it is just scientific investigation which we'll put up on the website and make available to people kind of thing.

DR. WILLARD: Yes?

DR. MAY: I guess I'd like to ask a sort of follow-up question, sort of a practical one.

Do all of you get your funding through the same appropriations committee? I mean, that may be the answer. If you have different appropriations committees, then it is kind of hard to control that. So all of your funding is coming through the same appropriations committees?

DR. GUTTMACHER: Well, NICHD is part of NIH, so yes, we get all of ours from the same committee. And CDC.

DR. KHOURY: I think (inaudible) funding through the same process. The VA is separate, isn't that right?

DR. FIHN: VA is separate.

DR. WILLARD: I have Joe, and then Debra.

DR. TELFAIR: My question is to everyone. I just want to say thank you for the excellent presentations. I did learn a lot from you. Maybe too much, but a lot.

The question I have is for those who presented on the very large studies. It is pretty obvious that there is a huge amount of responsibility that you have taken on to conduct the studies. One of the things that is important to know because it doesn't always get discussed, is at what level are you engaged, should I say, in some evaluative process about what you are doing?

There is the research process, but then there is the process of looking and evaluating. You have certain goals and objectives, but there is the side. Dr. Newton, you spoke about them, the big management and logistic issues.

I guess I'm looking at that as since most of you are talking about longitudinal studies, and most of you are talking about that you are going to have a lot of interaction with large numbers of people,

I'm just wondering whether or not there is something, an evaluative component to this side of the work that you're doing. If you have it, what are you doing? If not, why not?

DR. NEWTON: From our point of view, we have evaluation at every level within our company. We have all the committees, and we have the Ethics and Governance Council who evaluate certain elements. Funders, the Wellcome Trust, and the charity has its own review of what we do. The Research Council has also evaluative procedures.

We are extensively interrogated by the Parliamentary Science and Technology Committees. We have the groups who continue looking at what we're doing. We are committed to open publication of all of our science, so we have scientific peer review. Ultimately we would involve the participants, but we haven't got participants yet.

I think one of the things, it is difficult to know how successful the projects will have been for many years. So there is a sort of long-term evaluation that is important.

DR. TELFAIR: Yes. I think my question had to do more with the formative types of evaluation, which is long term, which is looking at the process as you go. You have a number of steps, a number of sort of targets along the way, milestones along the way that is telling you whether you are successful or not.

There was not a lot of discussion about that beyond these regulatory types of oversight. But just for you as involvement in projects, it is pretty critical when you do this, particularly when you are dealing with social and ethical types of issues, and you also interact with the persons you're dealing with. That's my question.

DR. GUTTMACHER: I can say we were certainly aware of that, and partly because we have learned from discussions with John about what Biobank has been up to, but others as well.

We are also influenced by the Human Genome Project. We are a hallmark of doing that kind of large coordinated longitudinal science in some ways to have clear benchmarks along the way that one wouldn't just sort of wave at and say we met it or we didn't, but in fact that there were, and there were various folks that were funded along the way that will tell you that there were real results from whether or not one was meeting one's benchmark. So that in fact there would be expectations for that in various kinds of ways, including for various kinds of community participation.

Those who will be looked at along the way, and one would react to how it is going in terms of reshaping the process as you go. It's absolutely important for something of this magnitude and length.

DR. WILLARD: We have one final question, and then we're going to have to wrap up.

Debra?

DR. LEONARD: Well, it's supposed to be one final question, but I am so excited by this possibility of doing this in the United States.

I am more interested with the specimen access at the end. I haven't heard a lot of discussion. I saw the pictures from the biobank of this retrieval process for investigators.

Are you giving out specimens? Then I hear sequencing. Are you going to sequence and HapMap all the genomes of all the participants? Or the genome of each of the participants, and that data will be available, but specimens won't? And then the people would be recontacted if they wanted to participate in certain studies, because that was also mentioned as a possibility.

A final question. Is it feasible to collect specimens over time? Because, Alan, you mentioned that you could identify early disease biomarkers potentially, but you can't unless you are collecting specimens over time. So you have a specimen, rather than just at enrollment. But that may not be feasible logistically from a storage perspective, or from a financial perspective, but it would be a shame to not even consider that as an option.

DR. GUTTMACHER: Yes, and Teri, you might want to jump on some of this.

But absolutely the idea was that there would be samples gotten at baseline, but in fact one would get various kinds of samples when one sees people back. It might not be the same sample for everyone. Of course, there will be incident cases that happen during the study which might obviously guide you in terms of what you collect. But the idea is in having access to people periodically, you have the access to potentially get more samples.

As both the science advances, depending upon what the financial situation is, also the idea would be that if one is thinking about a long-term study, that with the pricing of sequencing obviously coming down with use of haplotype and other kinds of things, the sequence-only part of the genome, as David nicely took us through earlier, that one could imagine in fact having genotypic data on folks that was available, that was stored. So it is no longer a sample, it is a data set.

That data set would again be stored, but then shared with folks who had IRB approval to use it kind of thing. So very much like HapMap or something like that, the data would be made freely available. Samples are obviously both in terms of finances and in terms of a fixed volume. It is harder to think about how to share, but that doesn't mean there aren't ways to do it.

DR. WILLARD: John?

DR. NEWTON: Yes, we will send the samples out to a limited number of accredited laboratories, and then the researchers get the results. But the results are fed back into the resource. So it is an important point that as people use the resource, the amount of data in it grows, and it is made available to everybody.

DR. LEONARD: But can the specimens then therefore be used up? Are there problems with freeze thaws from -80 of these specimens? Are they stored originally as aliquots?

DR. NEWTON: Yes, that's why we have got so many aliquots. We are hoping to try and predict as far as possible to meet the needs of the researchers, so each specimen is subaliquoted.

It is very important that you send the samples to laboratories that are only going to use very small amounts, which means limiting it to a relatively small number of labs.

DR. WILLARD: Wonderful. Well, thank you again to the panel, both for your formal presentations --

(Applause.)

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