U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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

Sixth Meeting

Tuesday,
March 1, 2005

Grand Ballroom Salons A-B
Marriott Bethesda North Hotel and
Montgomery County Conference Center
5701 Marinelli Road
North Bethesda, Maryland

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P R O C E E D I N G S (8:39 a.m.)

DR. TUCKSON: I think we're getting close to having our slides ready for the presentation, so can I call the committee to order? I thank everyone for being here on Day 2.

Webcast, are we okay? All right. We'll go ahead without webcast for the moment and you'll catch up with us as we go.

Let me thank everybody for a very intense day yesterday, very hard work, and there are a couple of things we want to let you know that are germane. The discussion on coverage and reimbursement, there has been some subcommittee work last night and this morning, and at lunch time we will have a working lunch and we will present to you a schemata for, we hope, an organized and very precise discussion that will get us to some conclusion at the end of the lunch session. It will take everybody really paying attention and working hard to get there, but we believe that we can accomplish what we need to accomplish during the lunch hour.

To facilitate a working lunch, you have at your desk the Meritage lunch menu. You need to fill that out and we'll pick them up at the break, because by 10 o'clock, we have to have all the food ordered so you can get your food and be able to come back in here and work. This is a

critical, small ingredient that we want you to attend to.

With that, let me also let you know that at the break, by the way, we were shooing away people from the little food cart there, and it turns out that we don't need to shoo you away. Now, you're not supposed to bring bags with you, but that's actually available for everybody at the little food area out there. It's okay. People in the audience, you can get coffee out there and so forth and so on, and we're not going to be shooing you out. Just, as I said, don't bring your lunch pail.

Today from 8:30 to 2:45, we're going to talk about "Large Population Studies: The Opportunities and Challenges." Now that the human genome has been sequenced, scientists, clinicians, and society are all faced with the challenge of translating the wealth of information into improved health. This will involve deciphering environmental and genetic components of common complex diseases, large population studies focused on genetic and environmental factors in common diseases, as well as the interplay of those factors. These studies have been proposed as an important and perhaps necessary way to translate the human genome sequence into useful clinical and public health strategies. While many different approaches can be taken to such studies, all intend to build on the information provided by the sequencing of the

genome.

These studies are complex and they raise a number of scientific, logistical, and ethical and legal and social concerns. We decided, during our priority process, that it was important to understand the opportunities and the challenges posed by these large population studies and that these questions required in-depth study. NIH has also asked us to provide our feedback on the need for such a study.

As such, the Large Population Studies Task Force was appointed in June of '04 to begin work on this issue, and I'd like to thank the task force members for their efforts in organizing this session. Hunt Willard, who chaired it, Chris Hook, Debra Leonard, Ed McCabe, Joan Reede, Ellen Fox, Alan Guttmacher, and Muin Khoury all were members of that committee, and we want to thank you.

We also want to thank staff, particularly Amanda, as well as Holly Campbell-Rosen, for their work in organizing this session and developing the backgrounder that we have been supplied.

By the end of this session, we hope to have gained a deeper understanding of what large population studies are and why they are under consideration at this time. The goals of the first three presentations are to inform us about different approaches to large population

studies and provide us with a broad introduction to this topic.

We are very pleased that David Goldstein will discuss the conceptual basis for these studies, that Gilbert Omenn will present the public health perspective, and Teri Manolio will present an overview of national and international large population studies.

I would urge you to turn to Tab 1 of your briefing book and you will see the biographies of each of these three distinguished people, and so I'm not going to go through those right now.

To begin, let me just thank David for coming, and we are very interested in the next half an hour to hear you talk to us about the conceptual basis for large population studies of human genetic variation and common disease. David, thank you and welcome.

By the way, folks, I think what we'll do, depending on how long the presentations take, I think if they stick to their half-hour allotment, what we may do is if you have an urgent, burning question that you want to ask the individual speaker, we can probably take one or two of those right after, but then we'll also try to query the panel later.

DR. GOLDSTEIN: Well, thank you very much for the invitation to come here and talk about the conceptual

basis for large population studies.

What I'd like to do in half an hour is try to cover two things. One is why we might want to undertake such an enterprise, and secondly, how we might go about it in terms of what the technical requirements would be. I'm going to kind of bounce back and forth between those two things.

But kicking it right off, why we would want to set up a powerful framework for studying the genetics of common diseases, the basic motivations are indicated there. We would like to be able to predict risk, but importantly, and I'm going to come back to this a few times, we would like to be able to not only predict risk, but do something about it. It's not really good enough just to predict risk. This is not for insurance companies. It's not good enough just to predict. We have to be able to intervene. So that's something that's going to up, I think, in a few places.

The other motivation is not about prediction and intervention, but it's about identifying genes and pathways that might help us in the drug development process.

Finally, the aim would be to identify genetic determinants of treatment response, and that's traditionally thought of in terms of pharmacogenetics,

which I will talk a bit about, the genetic determinants of what drugs are safest and work best for a given patient, but you can also think about the genetic determinants of other kinds of treatment responses, such as when there options for surgical procedures and non-surgical procedures and so on. So in general, in the genetics of treatment response.

So the first thing that we need to be clear about is what kind of genetic variation we're talking about, and the first thing that needs to be said is we're not talking about the kind of genetic differences indicated on the slide here, where you've got a mutation that is segregated in a family that causes a disease. So in that simple Mendelian case, there is a 1:1 correspondence often between a genetic difference and the disease that we're interested, and that's actually quite straightforward to work with genetically and the community is now extremely good at finding those kinds of causes of disease.

Now, unfortunately, common diseases aren't like that. The genetic contributors to common disease don't have that kind of 1:1 correspondence.

So the kind of genetic variation that we're talking about here is illustrated with this cartoon. The idea is that our genome is a big place. There are many places in that genome where individuals tend to differ one

to the next, and in fact there are now estimated to be more than 10 million common polymorphisms, and that is to say a site where the rare form has a frequency of more than 1 percent. There are more than 10 million of those different places in the human genome, and if you allow for rarer variants, then of course there are many more than that.

These variants, the different forms of many of these sites, we know often have very subtle effects. So they change physiology in some subtle way. That's very difficult to measure.

Then these variants influence the phenotypes that we're interested in -- that is, the kind of diseases that people get -- in some kind of complicated interaction, both with other genetic differences in our genetic makeup and with the environment. That's what really creates the challenge. There are a large number of variable sites in our genetic makeup. They interact with one another, they interact with the environment, and then ultimately they have some kind of influence on what we're interested in looking at, and that is the health of the individual.

I really just want, in walking through this, to emphasize that at the end of the day what we're talking about is the probability of certain conditions being influenced by these variants. The variants do not determine the conditions, and for that reason I think it

isn't really appropriate to talk about genes for diseases. We're not doing the same thing as we did with Mendelian disease. We're finding the gene for diabetes and the gene for asthma and so on. We are understanding on how genetic differences influence these conditions. So its a different kind of thing.

So that's what our aim is, is to understand how all those genetic differences that we have influence our health. That's the aim. It looks like it's going to be difficult. There is now really no question about that.

But what I'll now turn to is some of the technical requirements that we're going to need in order to be able to make progress. I'll spend the most time talking about the requirements to efficiently represent genetic variation.

There are two reasons for that. One is that I was explicitly asked to do that, but the other reason is that's where we're farthest along. When you actually hear people talking about the genetics of common disease, nine times out of 10, people are talking about how good we're getting at sequencing and genotyping and how much we know about genetic variation. We actually have gotten quite good at that side of it.

That's the easiest side of it by far. The difficult side is things that we actually haven't made much

progress on, which is knowing exactly how to measure in patients what we need to measure and knowing how to relate that to the genetic variation. That's the harder bit. So I'll spend more time talking about what we're better yet, and then just sort of telegraph what we're not so good at and some ideas about how we might improve on that.

So first, kicking off, the genome is a big place and it's got a lot of genetic variation and, as good as we are now at sequencing and genotyping, we can't simply get very, very large numbers of individuals that suffer from a certain condition and individuals that don't and exhaustively compare them genetically. We're not capable of doing that right now. We might at some point, but that kind of capacity has always been promised to be right around the corner and it never quite arrives. So what people have been thinking a lot about is more efficient ways to make these comparisons and more economical ways.

Something that's getting a lot of attention right now is called "haplotype tagging," which I'll now spend a few minutes talking about. The basic idea here is to find a framework for efficiently representing the genetic variation either in a region of our genetic makeup that you're interested in or in the entire genome.

I don't know how well you can see this, but what's shown here is a cartoon representing a stretch of

the genome. You could consider that a gene, and indicated are each of the sites in that stretch of the genome that differ, where there's a polymorphism.

So there are 12 sites indicated there, and I'd just point here to this green group. Those are four polymorphisms that are indicated in the gene, and so you the first row is one chromosome you might sample from the population, and in that chromosome, that find site has a T allele and then the fifth chromosome you might sample from the population has an A allele there. Then you've got the next polymorphic site which has the alleles that it has and so on.

The point here is that members of the green group are all associated with one another. So in this case, if you know the allele that's present at the first sites, it tells you the allele that's present at the second site in the green group, and the third, and the fourth.

Now, those associations among variable sites in our genome are due to a whole raft of population genetic forces which I won't go into, but they do exist. There are these associations. They're usually not perfect. I'll say something about that in a minute.

But they do exist, and because of that, if you were interested in looking to see if any of those sites associated with a trait you were interested in, you would

not have to directly assay all of them. You could assay one member of the green group and it would tell you about the others. You could assay one member of the pink group or whatever color it is and it would tell you about the others and so on.

These associations are called "linkage disequilibrium," and so another name for this is linkage disequilibrium mapping, but the point is these associations do exist and if you understand the nature of these associations, then you know how to select out a subset of the variable sites that tell you about the others.

In this particular case, obviously the subset that you can use is one member of each color group, and there is no loss of information at all because each member is telling you about the others. So if one of the ones that you did not assay was influencing the phenotype, you would still see it through the one that you did look at.

So that is, at its conceptual core, the entirety of haplotype mapping or linkage disequilibrium mapping, and it is in fact the primary motivation, I think as far as I'm concerned and most people are concerned, for the HapMap Project, which is an effort to characterize these patterns of association among variable sites, so that you can select out a subset that efficiently represents the variation in our genetic makeup. So that is an extremely

important tool currently because we can't look at variation comprehensively, and that's the conceptual core.

Now, in fact the association, because we're doing biology here and this is not physics, these associations, of course, are never perfect. So you actually have to use a whole bunch of messy statistics to go through this step of choosing one member of each color group, but that really is a technical detail. This is the basic aim.

What I'd now like to do is just take a couple of minutes addressing the issue of how well we expect this work. So can we feel comfortable that we really do have a good framework in hand for efficiently representing variation? I'm going to try to give a yes or no answer to that question.

I'll illustrate that with some work that we did on a data set that we collected together with GlaxoSmithKline, where we looked at these patterns of association among 55 genes that encode major drug metabolizing enzymes. There were a bunch of these variable sites or polymorphisms that were assayed in a number of individuals, both of European ancestry and Japanese ancestry, throughout all of these genes. So that's the data set.

This just indicates the way that this sort of

analysis is carried out. This is the stretch of sequence indicated and there are genes indicates, and there are all the polymorphisms indicated that we looked at as thin lines. Those are about 60-plus of them spread through four genes that are contiguous.

What you do is do a statistical version of selecting one member of each color group and you identify nine out of those 60-plus polymorphisms that you assess are able to represent the other variation that's there. Then the question that you want to answer is, well, how well is that really going to work in representing variation that, A, you don't yet know about, and B, variation that's in a somewhat different population from the one that you looked at originally?

That's important because you have to remember that the way this works -- for example, the way that we're all going to use the HapMap data, is the HapMap looks at a number of individuals, for example, from the SETH repository -- so these are individuals of North European ancestry -- selects these special tagging SNPs, and then goes and applies them in a different group. For example, our case, patients with epilepsy and so on. So you have to ask the question how well will they represent variants that you may not know about initially and in a somewhat different population? So you need an answer to that.

So in this case, we find these nine SNPs to represent all these others, but what you want to know about is how well they represent SNPs that you actually don't yet know about and in a somewhat different population. So you think of statistical ways to do that, which I'm not going to talk about, and evaluate how well they do.

We went through a few of those exercises, which, as I said, I'll skip, but what I'll do instead is show a direct evaluation of whether or not they work, and that is taking these SNPs that you identify out to a brand new population sample and assessing whether or not they predict variable sites that we know are functional. So there are in these particular genes lots of sites that we know change the activities of the enzymes, for example. Those are exactly the kind of differences that we're looking for and we can ask do these tagging SNPs work?

This shows the result. Shown here is the minor allele frequency of the SNPs that we're trying to predict, that we're proposing not to type, and here is a measure of how well we can predict them. It doesn't really matter how that measure works, but what does matter is that if you're up here at the top in this performance measure, that is exactly the situation, and you can show this formally, of the cartoon. If you're up here at 1 in this performance measure, it's exactly like taking one member of each color

group that exactly predicts the others with no loss of power whatsoever.

If you're in this range, you do very well, and if you're down here you do very badly, which is to say that if there was a SNP down here that you did not type and it was influencing the condition, you wouldn't see it.

So how do you? Here's the minor allele frequency of what you're trying to predict, here's the performance, and once you're above about 5 percent, you do great. So it's fair to say the short, non-technical version is that out here, if any of this stuff was influencing the phenotype and we only typed our tagging SNPs, not these things directly, we would still see it. So that is really encouraging.

This is the very discouraging note. It's a small sample size so far, but the very discouraging note that these rare things may not be predicted at all. Sometimes you predict them and sometimes you don't.

Now, we've gone on and done a bit more of that kind of thing, and our impression is that this is a fairly general outcome, that in this framework you just can't reliably pick up the variants that are rare in the population, where rare is something between 3 and 5 percent as a cutoff. More work needs to be done, but that's how it looks to us at the moment.

So what's the conclusion from that? What I'd like to emphasize is that we are talking about a truly dramatic economy. In the 55 genes that we looked at, we estimated that there 4,000 common polymorphisms, and what we show is that about 200 of these specially selected SNPs can represent the other 4,000.

Now, you can select these in different ways and some people would use methods that would result in a number slightly larger than 200, but it is really dramatic economy that you can achieve this way, and I would assert that it is now not controversial whether or not you can represent common variation in this framework. It's still discussed a little bit in the literature, but I think that debate really now has gone out of date. I think it should be viewed as demonstrated that this framework can officially represent common variation.

I should say that I have no association with the HapMap Project, so I don't feel any need to support the necessity of the HapMap Project. It's just a technical evaluation. That framework really does seem -- not seem. Has been demonstrated to work well in representing common variations. So I think that's really encouraging, and of course, these data that we have are by no means the only data that make this case.

So common variation can be efficiently

represented. We should view that as non-controversial.

It seems unlikely that rare variation can efficiently represented. So for that, we don't have an economical approach. If we want to also identify the rare variants that influence both common diseases and responses to treatment, we're going to have to do more difficult, more expensive things, and we should because, without a doubt, rare variants will also contribute -- I'm not going to go into that whole debate, but I think it's quite clear to most people that both common variants and rare variants contribute to common disease. The relative importance of those two things, we don't know, but they're both going to make some contribution.

So we have a very economical method for representing common variation. We don't for representing rarer variation. I don't expect that tagging will actually serve the purpose, but you may find more clever methods to do it perhaps, and we probably need to think about alternatives.

So I think in terms of representing common variation, the genetic side, we really are now in pretty good shape. Even though we've got a challenge for rarer variation, it's terrific that we can now start asking questions about those 10 million genetic differences among us all. That's terrific. That's a real tool that will no

doubt lead to advances.

But what is much, much more complicated is deciding about how to look at individuals that are being studied genetically, both individuals that have diseases and individuals that don't have diseases.

So for example, if you're thinking about prospective studies, and many people have been making arguments for the advantages of prospective studies, and that is where you enroll people that are random samples from the population, for example, in one design and monitor them over time, and as they become affected by different common diseases, you can then carry out genetic studies knowing about the background of the individual because they've been in your study for awhile.

So as we move to carrying out those kinds of studies, which do have a lot of advantages, we need to think about exactly what information we need about individuals at the time of enrollment, and I don't have time to go into details here, but I would say that that's something that we really don't have a very good idea about.

For example, if you're interested in cardiovascular disease, exactly how much information do you need at the time of enrollment for a large population sample in order to understand the state of the person when they're 50 well enough that it really tells you extra

things about why they had a heart attack when they were 66? And we don't know exactly what we should be looking at when we enroll individuals for cardiovascular disease or for other things. We really don't know.

So if we move towards very large prospective population studies, that's something that we're going to have to figure out. Obviously, lots of people have ideas about it, but it's not like the genetic side where we really know what we're doing. It's definitely an area of active work.

The other thing I'd like to raise as an issue is the question of what types of information are the most important. For example, we've been carrying out a variety of studies in epilepsy, and a common way that people have been thinking about doing epilepsy work is the sort of thing that people usually do, which is you get a lot of individuals that have epilepsy and you compare them to a lot of individuals that don't have epilepsy.

Yet epilepsy has quite a striking potential, in that in cases where patients don't respond to pharmacological treatment, surgery is carried out and the actual affected tissue is then available for study, so that you can look at the seizure-focus tissue in those patients that have to undergo surgery.

That is basically not being done in epilepsy

research, and you can actually write out a long list of striking opportunities like that if we look at the right place and interface correctly with the actual care, clinical care, of patients where we might really figure new things out if we actually look at the right kind of information, and sometimes that right kind of information doesn't come from simply enrolling a million people in a study.

I'm not disparaging that. I'm saying there are other kinds of data that are available that emerge from clinical care that we are not making systematic use of. In the area that I'm familiar with, it's certainly the case, and in a variety of other areas. So I think we have to think very carefully about how we interface genetics work with health care to make sure that we really do capitalize on the most important types of information as, for example, we most certainly are not doing in epilepsy, although, of course, we're trying to change that now.

Another point that I would like to raise in that context is the overwhelming importance of having detailed information about how patients respond to treatment. I'm not going to have a lot of time to talk about this, though I'm going to talk a little bit about it, but I think that it is now very, very clear that genetics plays a major role in influencing treatment response -- in

particular, responses to medicines -- but in order to make progress in identifying the genetic differences among patients that influence how they respond to medicines, it is essential to have very detailed information about what medicines they were given, in what doses, in what combinations, and exactly how they responded. So we're not going to be able to make progress unless we have that available and that's very, very difficult to get.

In that context, I'd like to mention that one opportunity for getting that kind of information may in fact be through managed health care providers. Where the patient records have been electronic, that may be a framework for getting exactly the kind of information about drug response that you need. But in thinking about very large population studies, I would say that it is absolutely essential to make sure that you do the best job that you can do in representing how patients respond to medicines.

So I'd like to just end in the last four or five minutes with a couple of thoughts, A, about what we're trying to do, and then B, about the case for more serious attention to pharmacogenetics.

First, on the point of what we're trying to do, I would like to just raise the issue that in academic genetics research there's been a real focus on a final and accurate determination of whether a given polymorphism

really is a risk factor for a given disease. In some contexts, that's something that you would like to know. For example, in prediction, you would like to know whether a polymorphism really is a risk factor, but one thing I think that's not so well appreciated is that there are contexts where you don't need to know with certainty whether a polymorphism really is a risk factor. It's good enough to have an educated guess.

Now, I'd like to make that point by a reference to a project that GlaxoSmithKline has carried out, which I have not been involved in, but I report this with permission, and what they've done is done a genetic study comparing individuals with and without Type 2 diabetes, and they've tried to identify polymorphisms that are associated with diabetes. What they did is they looked at 400 individuals with diabetes first and 400 individuals without, and then they had a follow-up.

The size of those studies, and we know this already from calculations you can do in advance, are not sufficiently powered to reach a final determination with any degree of statistical confidence that a given polymorphism really is a risk factor for diabetes. In fact, reaching that final point of confidence is hugely expensive in diabetes because we know that the effect sizes are small.

However, what they did come up with is a set, when they went through that exercise, of 21 gene variants, genetic differences, that appear to be associated. None of those 21 clearly, with statistical confidence, is in fact a risk factor, but you can ask the question in a somewhat different way. You can say I don't care about any single one of those. I care about the set of 21. What is the probability that at least five or six out of the 21, even though I don't know which one it is, really are disease-associated? That's a completely different calculation, and in fact, in this case, what you find is that probably, with fairly good confidence, five out of the 21 are real, but you don't know which.

Now, that's actually still very useful, because in the context of drug development, that means you can take all 21 and start working on them. You don't have to know exactly which one it is, and you could ask the question if it's going to cost you another $250 million to get really precise assessments for each of those 21, maybe it's actually better to spend $100 million and start screening some of them.

So what I'd like to point out is that when we're thinking about drug development, it is not necessarily always just a matter of reaching a final conclusion, no matter what the cost is, of whether a given

polymorphism is in fact a risk factor.

And the ending, two minutes, is the case for pharmacogenetics. I think that in academic research, as far as I'm concerned, there is a slightly inappropriate overemphasis of studying predisposition directly as opposed to treatment response. It's starting to change, but I think it hasn't changed enough, and I just want to make the case that variable responses to medicines is, A, hugely important, and B, easier to do than directly studying disease predisposition.

So these numbers, the study that they're based on has many methodological issues and they are highly debated, but nonetheless, however you look it, it's quite clear that variable responses to medicines is hugely important. It has been estimated that adverse reactions to medicines cause over 100,000 deaths in the U.S. alone, ranking as the fourth or fifth leading cause of death.

In terms of variable efficacy, as in fact a senior vice president for GlaxoSmithKline pointed out, medicines typically don't work. So the average rate at which a given medicine does what it's supposed to do is about 50 percent. It varies across therapeutic areas, and a lot of this variation is genetic. We know that, but we haven't found it.

So I'd just close by saying that when you

actually start looking in detail at the genetic determinants of drug response, what you find out is that it's usually quite a bit simpler than the genetic basis of common disease.

That has two components. One is that you often know where in the genome to look for possible genetic determinants of drug response, and two, the genetic determinants of variable drug response often are common. So they are not the rare things that are hard to find.

The final point is that when you find a genetic determinant of variable drug response, there is often the possibility of doing something about it clinically. The possibility. It's not immediate, but you often, for example, have the possibility of suggesting that you use Drug A instead of Drug B or that you change the dose.

That, as a final point, is in sharp contrast to predisposition studies of common disease, where sometimes you find things that really are risk factors and there's nothing whatsoever that you can do about it. For example, ApoE4 is the classic example of that. Certainly, that doesn't mean we shouldn't do common disease predisposition, but it does certainly mean that in thinking about these large population-based studies, we've got to take the drug response side and treatment response side more generally very, very seriously.

I'd like to end there, and I should mention the people that worked on some of the stuff that talked about. Thanks.

DR. TUCKSON: Thank you very much. Very well done.

Is there one hot, burning question? If not, we'll come back and do it at the panel.

(No response.)

DR. TUCKSON: David, thank you very much.

Gil Omenn, terrific to have you with us, and we're looking forward to your perspectives on the public health point of view on large population studies of human genetic variation, the environment, and common disease.

For our speakers, by the way, just so you'll know, there is a little timer that's sitting right beside Sarah, and if you want to gauge where you are, it's there with the usual yellow light.

DR. OMENN: Thank you very much, Reed.

It's a great pleasure to join you. This is a scenario in which I've been intensely interested for decades, at least 35 years in pharmacogenetics and ecogenetics. So the chance to at least share with you how I think about think this and how I think many people in the public health sciences and public health practice think about the opportunities to really make a difference as we

expand our knowledge base from genetics and other fields is especially welcoming. Thank you for having me.

So here is a visual image which actually is a short-term vision, but we'll carry on for decades of work. As you've just heard from Dr. Goldstein, we already have the beginnings of an avalanche of genomic and genetic information, validated SNPs, the beginnings of a haplotype map for applications, candidate genes and alleles, and especially many candidate genes and alleles for particular disease risks.

The second bullet has been very much less addressed, and this is the improvement of our environmental and behavioral data sets and, most importantly, their linkage with genetic information. In fact, we have many proposed statutes and regulations that would make this impossible. I'll come back to that at the end.

The third is, of course, to carry out both of the first two items with well-established and, in the public mind and the legal mind, creditable privacy and confidentiality protections, both for genetic and non-genetic information. I'll come back to that also.

Finally, I think we can be quite confident that the technologies we have in hand and the concepts that are being developed will yield breakthrough tests, vaccines, drugs, behavior change schemes, and regulatory actions, all

of which would be aimed at reducing health risks and treating patients cost-effectively in this country and globally.

You know, in medicine, we say we save one life at a time. The School of Public Health at Johns Hopkins has adopted this wonderful logo: "We save lives millions at a time." That's the public health perspective.

The world in which we live is well known to all of you here. We're very excited about the new biology. Most of us recognize that many of the developments in the biology have been made feasible, even conceivable, by new technologies.

You know, there's this notion you go from science to technology to application. Well, there's a huge feedback loop from technologies. This is reflected in gene expression microarray, comparative genomics, proteomics, in which I'm working intensively these days, bioinformatics and computational biology, and on the medical side, and increasingly the community health service and public health preventive service's side, we talk about evidence-based medicine.

How many of you have heard that phrase, "evidence-based medicine"?

(Show of hands.)

DR. OMENN: Well, when we use it at a Rotary

Club talk or someplace else, you can see the mouths open, the jaws drop, and finally somebody articulates the question if this is exciting and new, what have you folks been doing up until now? It's a little embarrassing. But we're doing better. We're trying hard and, of course, sometimes the hardest sell is with our own clinical colleagues.

The vision from all this is a kind of health care and community-based services that would be personal, predictive, and heavily preventive.

This takes people prepared to carry out such programs. The Institute of Medicine two or three years ago issued this report, in which they stated "With the arrival in which we will have the ability to understand gene/environmental interactions comes not only the era of genomic medicine, but of genomics-based public health. Understanding genomics, therefore, is essential for an effective public health workforce."

The CDC is particularly well represented here today, appropriately so. Here are our centers that CDC established several years ago already, including one we're proud to have at the University of Michigan, another which I was pleased to help get started at the University of Washington, and the third in North Carolina. They collaborate effectively. They have a website you can

check. The mission is exactly the mission of this discussion.

Now, just so we're on the same wavelength and especially those who are likely to be aware of this meeting, and I'm not actually integrally involved, definitions do matter. There's something of a struggle over which is the broader term, "genetics" or "genomics." In quarters where I live and in some recent reports, we've tried to help the public and help ourselves understand genetics as the broader historical, broader scientific term of approaching genes and their roles in health and disease, physiology, and evolution, and genomics being the set of powerful new tools for molecular biology, biotechnology, and computational sciences that permit us, when we choose, to examine the entire complement of genes and their gene products altogether, although, as you've just heard, generalizing across all genes is a formidable task and we end up focusing pretty quickly.

These global analyses do permit us -- in fact, require us -- very usefully to go beyond what we sometimes speak of as "looking under the lamp-post," where we already know about a gene or a phenotype that we're most interested in or a desired effect from a drug and ignore the off-target actions of the same drug which lead to nasty complications and cost of the drug.

The same thing on the protein side. We can talk about individual proteins or proteins as a class. We can talk about proteomics, corresponding to genomics, looking globally at as many as possible of the very much larger number of proteins and protein forms that are coded for by those genes.

So we already had a good introduction to this subject about genomic information from the global analyses, the International HapMap Consortium, the direct associations of individual SNP alleles with various disease phenotypes, the very substantial database -- we heard it's now over 10 million -- and the haplotype structure work, which is really still emerging with a lot of clever efforts to use tagging SNPs and variable linkage disequilibrium, recombinant hot spots, and other details of haplotype structure.

Where can we get information about environmental variables to put together with the genetic information? Well, I'll give you a few examples, and you'll more from Dr. Manolio and others this morning.

The Centers for Disease Control National for Health Statistics has conducted for 40 years surveys of the American population and increasing numbers of laboratory analyses. Now, we're going to hear later and I will come to a slide about what is the set of categories called

"environmental" or "non-genetic" in the U.K. Biobank, but here I want to focus particularly on chemical, microbial, and, say, environmental exposures complementary to behavioral traits, reproductive history, and others which you will hear more about from others.

The NHANES, as it's now called, is proud of major impacts. It's a major contributing factor in the removal of lead from gasoline, one of the public health triumphs of the last century, elaboration of pediatric growth charts, prevalence estimates for cholesterol, blood pressure, hepatitis C, and other important variables.

These are the environmental exposures that are actually assayed currently in the NHANES, and this is ongoing. So lead in a lead biomarker in sites, cadmium, mercury, arsenic, organic chemicals, acrylamide, which is a reproductive and neurotoxin, phthalates, metals, IgE antibody showing latex allergy, aromatic hydrocarbons, phytoestrogens, dioxins, and a whole bunch of usually serological markers of microbial exposures. Also, cotinine for smoking history or, if a non-smoker, environmental tobacco smoke exposure, and a whole lot of other phenotypes measured in the laboratory.

So this is a rich data resource. Over the years, the NHANES II, which concluded in the '80s and had 14,000 people. NHANES III, 34,000 people. I actually

couldn't find in the very extensive website of NCHS the number for the current ongoing NHANES study. Muin Khoury told me that there will be about 6,000 or 7,000 so far who have DNA samples taken. I think that might be about a 10 percent sample of the total.

NIEHS is interested in environmental and genetic interactions. I recently have served on an Advisory Committee on Personalized Exposure Assessment. The approaches that we highlighted in our report, which will be out shortly in Environmental Health Perspectives, were the use of geographic information systems, and the example there is the NIEHS set of children's health studies, where they combined GIS and wireless devices to track exposures to pesticides to validate diary entries. These are diary entries not just of diet, but of activities and potential activities that would be tied to those exposures, including children who might be exposed as migrant worker families or children who would be exposed with concomitant information about pesticides in the house and garden, and they are developing spatial models for households at risk for lead poisoning and a variety of other exposures.

The second comes from the technology side of biosensors and nanoscale devices which will permit feasible measurement in the individual of exposures and relate then

to actual bioburden measures of the sorts that NHANES does.

The third category is molecular signatures of exposure, early effect, and variation to susceptibility, which we call toxicogenomics. The conceptual strategy here of really building a program which would fit very nicely with what was just described and what's going to be described in the Biobank and some other large prospective studies may be applied in proper settings to retrospective or nested case-control studies as well, of course.

You have to be able to identify what your priority diseases are and the plausible or hypothesized environmental factors. This is non-trivial. In fact, we basically punted in this study for later work to be done on this.

Identify potential genetic determinants, pathways, and model systems for exploring the genetic/environmental interactions. Identify target study populations for feasible measurement. Define the genetic determinants of susceptibility. Conduct targeted exposure assessments. Identify and validate biomarkers. Then try to bring this all together with genetic/environmental interactions.

One thing that should be emphasized is that the era of fighting between whether things are nature or nurture, genetic or environmental, is behind us. We're now

all thinking about contribution of genetic and non-genetic factors and specific ways they interact and even, I would say -- I cringed a little at the comment in the last talk that for Mendelian disorders, of course, we know exactly what the genotype/phenotype pattern is. It's a lot more direct than for multifactorial diseases, but it is also true that the variation can be quite stunning for single gene disorders, the most dramatic being reports over the last decade from Saudi Arabia and Jamaica of people with hemoglobin beta S homozygote status with no apparent phenotype, clinical phenotype, full biochemical phenotype, and many other examples.

Technologies and approaches. Some are listed here. I think I've already basically mentioned them.

This is natural process language to try to search the vast literature. There are some very good tools now becoming available for doing this in an automated way to us limited humans.

GIS I've mentioned.

Mapping and systems, and one of the questions I asked Muin was the extent to which the NHANES findings that sample all through the American population are actually being mapped as the EPA tries to do for other purposes to states, localities, neighborhoods, and maybe impute it all the way to individuals, and so forth.

This is one of the most important things for laboratory scientists, which is to link perspective sensors and molecular biomarkers in animals and in humans with in vitro and in vivo studies to try to make that between toxicology and epidemiology which has been needed for so long.

EPA. EPA, of course, regulates air, water, soil and, together with FDA, foods, food contaminants. The EPA has many measurement and modeling programs, of which this may be the most relevant for our purposes today. It's called the Multimedia Integrated Modeling System, MIMS. The primary application is to simulate ambient airborne substances in urban settings, and the spatial scales they are looking at range from 10 kilometers down to less than 1 kilometer, which gets to be interesting for imputation of individual exposures.

They are working on prototypes and successive generations of exposure modeling support tools, and this is both for air pollution and for homeland security. You can easily imagine that.

These tools bridge modeling gaps between two previously quite different approaches. One is the Eulerian chemical grid modeling and the other is the Gaussian plume dispersion models, which are prominent for water as well as air pollution. These models will capture temporal and

spatial variability at ground-level concentrations of air toxics. Also, hazardous releases from stationary sites, and may reveal enough hot spots to be quite interesting in terms of human studies.

There is a sort of progression to make ambient measurements in the air wherever there's a monitoring station, and where those stations are placed, of course, is highly irregular and never been systematized around the country.

There are personal monitors. We're familiar with these in the workplace, of course, in industrial hygiene, but they're available for community sampling studies.

There is biomonitoring, as shown here for several examples. Of course, with biomonitoring in isolation, as with NHANES, or with maybe the studies that are going to be done under these genetic population studies, there's usually very little information about the source of the agent that's measured, and that needs to be thought about in advance.

Finally, there's the National Scale, sort of the summation of all this, and the CDC in 2003 already did have 116 environmental chemicals, including the ones I listed for you a moment ago.

Here, John, is my take from the Web and from a

meeting I was at, a planning meeting in Dublin four years ago. I wasn't aware when I prepared my slides that we were going to have an expert talk about this from the people who are actually doing it, so I'll be very quick, but maybe it would be interesting to see the perspective of someone across the ocean about what we know about what's going on.

So this is a genetic databank to be developed from blood samples from half a million people. I understand that the studies will be based on proposals from researchers. The recruitment will be through general practices, many of them, in regional combines with a 10-year follow-up. The age at recruitment, 45 to 69, and there are expected to be substantial number of deaths over that period of time from common diseases, some of which would be of great interest here.

There will be a questionnaire for risks, lifestyle, diet, and there will be a blood sample taken. There's not been too much said yet about what the blood sample will be used for. Maybe we'll hear today.

Statistical power estimates. It's very important in planning studies, of course. They expect over 5,000 cases per year for diabetes mellitus, ischemic heart disease, myocardial infarction, colorectal cancer and breast cancer, and you can see here the projected relative risks and interaction ratios that they would be able to

detect with these numbers and that power. I'm sure that should be .01. So 1 percent significance. Then at a lower incidence, there would rheumatoid arthritis, Parkinson's disease, hip fracture, ovarian cancer, bladder cancer, and others, with, again, power estimates.

They have a very high expectation that 40 to 50 percent of the patients in each practice would actually enroll. This would be astonishing in America. Maybe they can do it in the U.K.

Now, they've chosen for the blood sample EDTA plasma. It's a very interesting question always of what form of serum or anticoagulant to be used. In a separate big international collaboration I lead about proteomics of plasma and serum, we have similarly given high grades to EDTA, but even higher to citrate plasma.

There will be nested case-control and cross-sectional studies, including a variety of family-based studies.

There have been some criticisms of the design, naturally. One is that even at half a million people, the cohort is much too small to analyze complex multifactorial diseases.

Heterogeneity within these disease diagnostic categories is extreme. When I was in Ireland, there was a big discussion about a proposal to actually enroll sib

pairs, which would be particularly informative for genetic studies. I'm curious what the status of that is. I couldn't find any mention in the website.

The cohort age of 45 to 69, of course, is a late time to be gathering information about the crucial determinants of early stages of latent diseases, long-gestating diseases.

Of course, relying on medical records, while maybe they are better than here, is still a limitation. There is some comment that there might be an overemphasis on genetic factors because of the reliance on the medical record and because of the lack of much collection about other kinds of environmental factors, and there have been vigilant consumer and patients looking out for confidentiality and opposing any kind of genetic behavior studies, and some other concerns.

These are the exposure categories, as I understand it. You can see them all listed here, and no specific mention of environmental chemicals, which in this country would be top of the public's list.

Examples of the kinds of studies that can be undertaken you see here. All of them are interesting, yet they're of a subset of the variety that I've been indicating would be a broader environmental/genetic interaction.

Now, other large-scale studies are underway in various places, and in the Biobank site they mention the much-publicized studies in Iceland and less publicized in Estonia and under development in Canada. There's a big European collaborative study called EPIC, and there are others which Teri Manolio I guess has provided those of you who received the materials for this meeting.

Now, in this country, the most remarkable study of the last decade has been the Women's Health Initiative, with 160,000 women participating in both observational and randomized studies, and as you know, the outcomes have been front-page news most months.

Now, let me bring this into a little broader perspective from the public health view. This is about genetics and environment and how we share a lot of interests. We both aim to bring together the digital code of inherited information with the environmental cues, some people call them, from nutrition, metabolism, lifestyle behaviors, pharmaceuticals and nutriceuticals -- don't forget the nutriceuticals -- and these chemical, physical, and infectious exposures.

The broad way to think about this is a systems biology approach that looks at the inputs, the perturbations, and then genomic, epigenomic, transcriptomic, proteomic, metabolomic levels of

integrating the molecular information.

Ecogenetics has been the focus of my talk here and I'm going to carry on for a few more minutes about environmental and occupational exposures and variations to susceptibility, but it can be looked at from the point of view of infectious diseases, chronic diseases, nutrition, unhealthful behaviors, and it means that we should include genetics prominently in protocols for health promotion and disease prevention, and these would include host/pathogen interactions as well as drug and vaccine development. I've already mentioned the training need.

Put all that together and there should be, in the next decade or two, really a golden age for public health sciences. We need these kinds of population-based disciplines in order to make sense of genetic variation. It would be a tragedy, in my view, if we had extensive genetic variation and really could not make the relationship to phenotypes or answer people's questions about what you could do with this information to reduce your health risks.

With regard to the chemical exposures specifically, there is a discipline of risk assessment, risk management, risk perception, and risk communication which has developed over the last 25 years. It's really all addressed at this question or this observation:

scientists disagree.

This is extremely bewildering and disconcerting to a lot of people. In fact, in this current debate about faith-based ways of thinking and scientific ways of thinking, the characterization of scientific ways of thinking as all based on fact and certainty is a huge failure of our communication because we are typically most interested in what we don't know and what is uncertain and how we could learn more and make it useful.

There's a framework for this kind of thing with regard to regulatory decisionmaking in chemicals, and other factors, too, but especially for chemicals to identify whether there's potential for hazard with all of these methods, especially the ones I've been talking about, to characterize the risk -- very important word, characterize, not just to quantify, but to describe, have a useful narrative about the nature of the health effects observed, the phenotypes and how reversible they are, how serious they are -- related to potency, exposure analysis, which until recently was very underexplored, and our point here, of course, variation susceptibility, and then to do something about it. Very often information, long before there's a regulatory action, has a powerful effect.

Toxicogenomics I mentioned. This is the signature program at the NIEHS, the National Toxicology

Program. There's a framework which says we need to put any environmental scare or scientific finding into broader public health and maybe even ecological context, and then have an orderly process of developing an assessment of the risk, reasonable options, make decisions, actually make decisions and carry them out, and evaluate what we've accomplish if we do. All of this, from the very beginning, with active engagement, proactive engagement, of stakeholders -- very important -- as the genetics community has been doing around our issues.

Context means, in the environmental world, going beyond the statutory scheme we have of one chemical, one environmental medium, one health effect at a time. Think about the total public health status of children or of any other group.

Intense requires multiple molecular markers and especially a public health comprehensive view.

Context means medical source of the same agent, number of pathways of exposure, multiple risks from one agent or multiple agents causing the same effect, data, surveillance, interaction with the environment, and crucial issues about health disparities, environmental justice, social and cultural traditions, and differences in perception about risks and what should be done about them.

Finally, I want to point out some good work

from an organization called Partnership for Prevention engaging with the states. Of course, CDC is very active with the states and other agencies. There's a lot of action at the state level. In fact, pending federal legislation on protecting people from insurance or employment discrimination for genetic diagnoses, some 38 states at least have passed their own patchwork of legislation.

Well, the aim for states is shown here. Monitor what's happening and to ensure that we have applications not just for treatment of people with specific diseases, but for health promotion and disease prevention.

These are the two key findings. The first we've already covered, that there's a lot of opportunity in this genomic era.

The second is a hot policy debate and it was the position of the Partnership for Prevention that genetics and genomics should be integrated into existing health, social, and environmental policies, rather than establishing stand-alone genetics programs. Maybe you don't all agree with this, but let me tell you why.

This is quotation from that report citing a very highly regarded report which I was not personally involved in at the State of Michigan from the Governor's Commission on Genetic Policy and Progress. "At a time when

many state policies were based on exceptionalism" -- that means taking genetics out from the mainstream of medicine and public health -- "Michigan adopted an integration perspective and recommended that genetic issues be dealt with in the context of overall medical care values and principles."

"All health conditions have some degree of genetic basis. It's very hard to draw a line between what is genetic and what is not. Most common diseases that we're emphasizing here result from gene/environment interactions. So genetic advances are likely to extend and expand, certainly not supplant, current practices in medicine, public health, and environmental protection.

"Some genetic variations are associated with greater health risk than others. Covering this huge range with a one-size-fits-all policy is inappropriate.

"Decisions about genetic policy involve complex issues about ethics, costs, benefits, individual and societal interests. Medical care decisions should be linked with research, insurance, and broader public health policies.

"The intersection between genetics and public policy is both immediate and long-term, warranting close monitoring."

I added this line on the bottom, which is that

in this era where in the clinic, where I will be all day tomorrow, we have to tell patients that it would be wise to make sure your insurance is complete and adequate before you have any tests done, and that prohibiting discrimination based on test results or genetic diagnosis is necessary.

The kinds of research we want to stimulate in populations and communities requires certain principles. Albert Johnson, a prominent bioethicist, observed in one of our seminars years ago in Seattle that while we had developed very widely accepted concepts and tools for ethics in medicine -- namely, the informed consent principle and the principle of autonomy of the individual participant -- that we had no corresponding highlighted principles for public health or community-based research.

So Jim Ledrefow and I and others developed and we published this scheme about engaging community partners early in the planning process, keeping them posted, seeking their input in the analysis and interpretation, building productive partnerships that last, and empowering people to propose studies.

There are sources of information shown here, and a final comment six years ago from Francis Collins that what we're engaged in collectively, mapping the human genetic terrain, may rank with the great expeditions.

It's clear that to get maximum value and meet our public responsibilities that we need to understand the progression from genes through proteins and some molecular and laboratory interests, and of course, clinical translation and, more broadly, to address the issue of this meeting, which is to link genetic variation with the many kinds of non-genetic variables.

Thank you very much.

DR. TUCKSON: Terrific. Thank you very much, Gil.

Again, any one particular question?

(No response.)

DR. TUCKSON: Thank you, Gil. We'll come back to you in just a bit.

Now Teri Manolio will give us a sense of the overview of this issue from the international and national perspective. Thank you so much, Teri.

DR. MANOLIO: Great. Thank you very much.

I appreciate being invited to comment on international and national cohort studies. There are a large number of them and we won't be able to do them all justice. Luckily, several will be discussed in more detail here.

So what I was asked to do was to review these studies and then talk somewhat more about design as well,

design of prospective studies versus case-control studies, design of phenotypic definition, and I probably won't have a chance to get to this last one, use of existing cohorts versus new cohorts, but if we time we'll do that as well.

There are, as I said, a large number of these. There are new ones sort of cropping up every day. Very few of them had actually gotten into the field and gotten going.

The Public Population Project and U.K. Biobank you'll hear about a little more from subsequent speakers, so I won't focus as much on them. Biobank Japan and Estonia I can talk about a bit, and this one I can go into a little bit more detail because it's actually the one that's furthest along and is generating results. I'll also comment on the Marshfield Project, you'll hear about the National Children's Study, and there are a variety of other clinical samples that I won't go into.

Just a broad overview of several of the international ones, the Biobank Japan, obviously in Japan, is anticipated to be 300,000 people ages 20 and above. The focus at present is on 47 common complex diseases, which, as we've heard before, were diseases that do not seem to have Mendelian patterns of inheritance that are related to a single gene, but probably to multiple genes. Access to those data and samples at present is limited to Japan and

Japanese researchers.

DeCODE Genetics was mentioned earlier. It's in Iceland. They anticipate having most likely the entire population if they keep going, at least all of those that consent, which would be at least 200,000 of all ages, 50 common diseases, and access is possible with collaboration.

The Estonian Genome Project in Estonia has varying estimates of the size. The total size of the country is about 1.3 million and they had initially talked about trying to get a million of those. Now they're scaling back a bit more to closer to 100,000. The age I'm not quite sure of. I assume it's all the adults, but I don't know. Common diseases, and again with collaboration.

Then you've heard much about U.K. Biobank and we'll hear much more about that.

CARTaGENE is a Canadian study in Quebec. It's anticipated to be about 50,000 people aged 25 to 74. Again, focusing on common diseases, and Mylene, who will be filling in for Bartha Knoppers, whose flight was canceled, will tell you more about that perhaps.

GenomeEUtwin, similarly, is part of that collaboration. It has seven European countries with 800,00 twin pairs. Twin pairs are a very interesting genetic model. They have great strengths, as well as some weaknesses, and I'm sure you'll hear about that. It's

focusing on seven key outcomes at present, and they are available with collaboration.

The Marshfield Personalized Medicine Project is in Marshfield, Wisconsin, relying on the Marshfield Clinic. It anticipates 40,000 people 18 and above with a very large focus on adverse drug reactions. David Goldstein spoke to you earlier about the importance of adverse drug reactions, and I think that would be a place, David, where you could find some really exciting information about this.

The National Children's Study Dr. Brenner will be talking about a little bit later. It's to include 100,000 infants and their mothers and to follow them for 21 years.

Just briefly to comment on Biobank Japan, the goal of the study is to clarify on a large basis the causes of diseases and medication side effects in relation to genetic variations and ultimately to develop new drugs and diagnostics.

The goal of many of these large biobanks is focusing towards drugs and diagnostics as a way not only to contribute to the field, but also to help support the biobank itself.

Samples and data will be collected and are being collected by a network of collaborating organizations and private universities. Public universities are not

involved in this one, and that has raised some eyebrows, as it were, outside of Japan, but the Japanese seem quite happy with it and it's their study.

These are some of the universities that are involved. The Tokushukai group bills itself as the "third largest hospital group in the world," and it does have a very large catchment area.

They hope that their project will stimulate the development of legislation in Japan to protect personal research information. Not only genetic information, but research information in general, which is an interesting sidelight to the biobank.

It was begun in 2003. Ninety-thousand samples have been collected to date, and that actually is 120,000 disease cases because each person that they've collected has more than one disease. This is unlikely to be a random population sample. It's more patient-based because it's working with hospitals, and so its relevance to a general population is a little more questionable.

Distribution of DNA and serum to Japanese researchers has already begun.

The Estonian project has a similar goal to find links between genes, environmental factors, and common diseases, and apply that to improved health care. There may be as many as a million persons, but now scaling down

perhaps to 100,000, and it was begun in October of 2002 with about 10,000 recruited in an initial pilot as of 2004 in three Estonian counties.

There is written informed consent, a 60 to 90-minute questionnaire that includes genealogic information at least back two or three generations, simple measures -- height, weight, blood pressure, heart rate -- and a 50-milliliter blood sample.

Personalized information is intended to be provided back to participants with their consent and with their interest, and to their physicians, again with their consent. The people who participant in this are called "gene donors," and actually participants can go on to their website in Estonia and ask a series of questions about their involvement and what it means for them.

There is a non-profit Estonian Genome Project Foundation which is in public/private partnership with eGene, Inc., which was a private arm. Actually, they have just recently dissolved their arrangement with eGene in 2004 and they're now looking for other sources of funding.

The Marshfield Project, as I mentioned, is based out of the Marshfield Clinic in Wisconsin, which is a very large private set of clinics. It's intended also to translate genetic data into knowledge that will enhance patient care.

It utilizes the Marshfield Epidemiologic Study Area in Central Wisconsin, which has a longstanding electronic medical record program, and so utilizes the strength of having ongoing electronic records. I would comment, though, that clinicians are still clinicians, even in Wisconsin, and they don't always record things in a standardized way. So just because it's electronic doesn't mean that it's reliable.

There are active programs in Marshfield in genomics and clinical research. They intend to recruit up to 40,000 people aged 18 and older. This was begun in September of 2002 and 17,000 recruited so far. Response rate is actually fairly respectable for a study of this size and scope, 45 percent. In epidemiological studies, we like it to be much higher, but for a variety of reasons, this is quite good.

There is written informed consent, a 30-minute visit with questionnaires, DNA extraction, blood. The data are encrypted, which means that there is no one with access to the identifiable clinic information has also access to the genetic information, and there's a link there that can be broken by a third party.

DeCODE Genetics is the Icelandic group. They are a biopharmaceutical company that are applying discoveries in genetics to develop of drugs for common

diseases.

They utilize the unique resources of Iceland, which is that, first, it's relatively isolated. It's an island in the middle of the North Atlantic. There are founder effects there, which means that they were settled by a relatively small number of people -- probably in the tens of thousands, though, still -- in the early 10th Century, and it remained isolated since then. They've also gone through a series of population bottlenecks, famine, disease, and volcano eruptions and things.

They also have an extensive genealogic database extending back to the settlement of the island in 900 A.D. They have a very small number of high quality referral hospitals and very good records.

DeCODE currently has DNA and data on 110,000 consenting Icelanders and about 25,000 non-Icelanders from various parts of Europe that they have collaborations with. It was begun in 1998.

There was tremendous controversy generated by this project, primarily because of their proposal for an opt-out consent for access to medical records. There was a proposal to have what was called a health sector database that would be accessed in everyone, and this opt-out consent did cause a big problem. That eventually was abandoned. The plans for that, whether they'll be

revisited or not in Iceland is not clear, but there has been written informed consent for all of the genetic studies, and there's third-party encryption as well.

I should, in the interest of full disclosure, mention that I am collaborating with this group. So that's partly how I know a little bit more about it, but you may want to take my comments in that context.

The uniqueness of this population, as I mentioned, they were founded by settlers of mixed Northern European descent from Norway and Sweden. They stopped off in the British Isles and picked up some passengers, sometimes willing and sometimes not, and went to Iceland from there.

The current population is about 285,000, which is almost exactly one one-thousandth of the U.S. It's about the size of the town of Framingham, which you may have heard of, and another tremendous resource is their careful genealogic records. Genealogy in this country is more than a national hobby. It's almost an obsession. I mean, they all know who they're related to. When two Icelanders meet, they'll say, "Oh, you're so and so's grandson. My cousin went to school with your aunt," and they can all relate each other to various and sundry relatives, and without any enmity or anything. It's not like there are feuds between clans and that sort of thing,

but it's clearly something that they're very interested in and have kept very good records.

So given the relatively small founder population, there is relatively similar genetic background, and their isolation following that means that there are fewer variants to study.

What has been done with these genealogic records -- which any family, if you visit an Icelandic home, they have books in their family and after dinner they'll take them out and show you how they relate back to various groups -- is these have been computerized, and every Icelander has a password to this.

This is actually the genealogy of Kar Steffenson, who is the founder of deCODE, and he can go into this, as can any Icelander, and trace his genealogy back one, two, three, four, five, six generations to this person. Then click on this next button, and she was born in 1776, and trace her back another six generations. Then the next one, born in the 16th Century, and in the 14th Century, and in the 12th Century, and finally back into the 10th Century. So back to their original Norwegian founders. Most of them can do this. It's really quite remarkable.

What they also can do is when they meet someone, they can go home and look them up in this

database --

(Laughter.)

DR. MANOLIO: -- and found out who they're related to and find out how closely they're related to each other. So married couples, it was very interesting when this came out. They were saying, "Oh, we're actually related back five or six generations. Maybe that's why our son Charlie is so strange."

(Laughter.)

DR. MANOLIO: More often, it's just an interesting hobby that they have. They're very interested in it. They'll say, "Oh, I can go home and check and see who I'm related to," and this is a big deal for them, so that's fine.

It's also a big deal for science because what one can do then is take two people that happen to have the same disease and see how they're related to each other and pull out groups of cases that actually are related in very large pedigrees.

That was done in our atrial fibrillation project. This is a pedigree with 69 patients. It's not the largest one that they had. There was one that was 700, but this one fit on the page.

What this shows you is that all these people with atrial fibrillation in these little black boxes and

circles, which are a tremendous resource then for finding genes, and the purpose of this kind of study is to actually identify genes related to common diseases.

What we did with this then, recognizing that common diseases don't show Mendelian inheritance patterns and very often you don't just have affected sibs, which is the model that's most often used in this country looking at sib pairs, but you often have people with more distant relatives. So you can look at the degree of relatives.

If you have a person with atrial fibrillation, his or her first-degree relatives are 77 percent more likely to have atrial fibrillation than people without a relative with atrial fibrillation. If you exclude the first-degree relatives, which are mothers, fathers, sisters, brothers, daughters, and sons, the relative risk is still 36 percent higher, 18 percent higher if you look at third-degree relatives, 10 percent, and 5 percent if you look at fifth degree.

Very few populations can go to this level of detail in relationships, and what's interesting about this particular example is that this decline by halves basically in degree of relative risk parallels the decline in sharing of genetic variants through generations. So it's a very strong suggestion that there's something genetic here that is related to this disease.

So deCODE has used this approach to map diseases, which means finding areas of chromosomes that are likely to be related to disease for all of these diseases shown in white here. For those shown in blue, they've actually identified what likes to be a causative variant. So within a gene, they've found the gene and the possibility of a variant related to it. Then these purple ones are things that they've actually developed drugs for and are in clinical trials to try to reduce. So again, a very powerful way for finding genetic variants.

Now, one of the challenges in identifying genes is to actually understand, as Gil was alluding to earlier, the population impact of these, and I guess I would quibble a bit with Dr. Goldstein's comment that just because you know a gene, you can't do anything about it.

ApoE4, for example, we actually know interacts with a variety of other risk factors in relationship to cognitive decline, and it may be that one would want to really reduce those other risk factors as a way of perhaps reducing the risk in someone with ApoE4. That's a reasonable research question that needs to be pursued.

But if you consider genes just to be risk factors passed from parents to children, epidemiologists know what to do with risk factors. Then you want to determine the prevalence of them. You want to look at

associations that are identified in family studies or other studies, and assess their magnitude and independence, recognizing that common risk factors are generally not strong ones and strong risk factors are generally not common. If they were, we'd all have them and we'd all be sick. So basically, those get weeded out and we end with the smaller effect, but that are much more common.

One can define associations with a variety of phenotypes. Not just atrial fibrillation, but perhaps as it's related to other diseases as well, and identify factors, particularly environmental factors, because these are the things that we can change. These are the things that have changed in the past 30 years to give us this incredible epidemic of obesity that we're facing. That hasn't been the genome that changed. If we can identify those things and have some impact on them, we may particularly want to do that within genetically susceptible individuals.

This shows just three of the variants that deCODE has identified. There is a little bit known on the allele frequency and the risk associated with these in the Icelandic population. The Icelandic population, for a variety of reasons, is very different from the U.S. population, and one would want to know not only the allele frequency and the risk, but other phenotypes and

associations are there with these particular variants? And particularly, what modifies them? Very little of that work has been done and that's what needs to be done in these larger biobanks.

Francis Collins published a paper earlier this year talking about the need for large cohort studies, and Dr. Guttmacher will comment on this a little bit later.

Identifying and reducing disease risk depends on an unbiased determination of a variety of things. The actual quantitative contribution of both the environment and the genetic factors, the interactions among them, and the interplay among other disorders that may share common risk factors. So if you get heart disease, does that affect your risk for asthma or cancer or other things? It probably does.

He recognized and pointed out that replication of associations and estimating their magnitude, consistency, and their time relationships is best done through prospective cohort studies.

Just briefly, cohort studies are prospective -- that is, from before the time a disease develops out into the future -- investigations of a representative sample, representative meaning that you can relate that back to the population from which it was drawn. So you're not just studying truck drivers who may be different from the rest

of the population. You're not just studying Air Force pilots. You're taking a sample that's representative of the entire group.

You follow them for development of specified endpoints. So you want to identify things and look for them actively, so that they don't just happen to be picked up, but actually are surveyed and picked up systematically.

The purpose, as mentioned before, is to identify risk factors predisposing to development of the disease in general populations. Particularly, you want this design when you're looking for risk factors that are affected by disease. So you can't measure them after the disease has occurred, the things that are affected by treatment or by lifestyle changes. When people feel sick, they might think I need to do something about it to prevent myself from getting disease, and so those things can then have an impact on the associations you measure.

You particularly want to look at those that are difficult to recall or in which there is biased recall once somebody develops a disease, and we'll talk about that in a minute, or with hypothesized early pathogenic effect. So something that has an impact early on and then later on may not have much an effect at all, you're likely only to pick those up in prospective studies, rather than waiting until the disease occurs.

And they complement a variety of other epidemiologic designs which I'll talk about, particularly case-control studies.

Again, in the interest of full disclosure, I should mention that I'm responsible for the group at the Heart, Lung, and Blood Institute that runs major cohort studies, such as Framingham, Honolulu, and a variety of others. The sample sizes are shown here and the ages, and fortunately we're doing a little bit better in including minorities, but that has been a challenge.

Pros and cons of these kinds of studies. They are very expensive, they take a very long time, you need large numbers of people, and they're very broad-based, and so there tends to be a lot of criticism of them as being fishing expeditions, et cetera, et cetera.

They, however, provide risk information that really you can't get any other way. Healthy people don't typically go to the doctor, and they don't get screened and they don't get their risk factors measured, and if you want to understand why healthy people get sick, rather than why sick people get sicker, what you need to do is a prospective study.

In general, the public is better able to understand these than often with clinical studies because you can relate to the people. "Gee, that's somebody just

like me. That isn't somebody that was exposed to beryllium," or whatever it might be. "It's somebody just me living in a community. I can understand that."

They identify modifiable risk factors that might be intervened upon, which is what we're in this business for anyway.

If you wanted to look at the characteristics of ideal cohort studies, size is very important. The larger, the better, up to some degree, obviously, because when they get to be too big you may not be able to actually measure enough on them to make them worthwhile.

They should be representative. They should be diverse in geography, in this country, at least, socioeconomic status, and race/ethnicity.

There should be standardized and reproducible characterization of exposures and risk factors. Ideally, there should be repeated interim measures to check differences or changes in risk factors and exposures over time, and comprehensive standardized assessments of outcomes.

If one doesn't do this, particularly the standardized aspects of it, you're prone to a variety of biases that can affect your study results and lead to basically erroneous conclusions. I've mentioned a number of them here. Several of these are particular problems in

the case-control study design, and case-control studies have gotten a bad name mainly because I think people haven't followed appropriate design strategies for them.

These are three assumptions that one has to basically meet in order to have a well-done case-control study. The cases are representative of everybody who developed the disease. Not just the people who go to Hopkins, not just the people who drop dead, but everybody.

Controls are representative of the general population that don't develop the disease.

Most importantly, collection of risk factor and exposure information is the same for cases and controls. This can be a real problem because once somebody is sick, it affects the way they recall things and the way they report them.

The advantages of this are it may be the only way to study rare diseases.

Existing records can often be used if the risk factor data are collected independent of disease status, and that often doesn't happen. Once somebody has lung cancer, you ask them 1,000 times if they smoked and were exposed to asbestos and that sort of thing.

You can study lots of etiologic factors, and they may be less time consuming and expensive.

Disadvantages are that they rely on recall or

records for information, and validation of these past records can be very, very difficult. Selecting an appropriate comparison group can be tough, multiple biases, as we talked about before, can get spurious evidence of associations, it's difficult to study rare exposures, and it's difficult to study temporal relationships.

Now, it's usually at about this point in a conversation with geneticists that they say me, "Now, wait a minute. This is genetics, you dumb epidemiologist. This is different. Genes are measured the same way in cases and controls. No bias there." Information on your key exposure of the genes, then, is very easy to validate. There's no recall or reporting and temporal relationships are very clear.

But in response, I would say that bias-free ascertainment of cases and controls is still a major concern. Cases in most clinical series are very unlikely to be representative and assessment of risk modifiers or gene/environment interactions is very likely incomplete or flawed unless you have done it in a prospective way.

But this is a very, very powerful design. If you look at a disease with an incidence of 8 per 1,000 among the unexposed, which is a relatively rare disease, a cohort study would require 4,000 exposed and 4,000 unexposed people to detect a two-fold increase in risk. A

case-control study would require only 200 cases and 200 controls with a 30 percent exposure. If you then look at disease that's a quarter as common, 2 cases per 1,000, you need 16,000 exposed and 16,000 unexposed to detect that same degree of risk, but a case-control study still requires only 200 cases and 200 controls.

So this is a very powerful design, and what to do, and I'll finish up in just a moment, is to nest this kind of study within a prospective study, so that you identify cases as they develop and them measure on them things that would otherwise be very expensive to measure in an entire cohort, because a large proportion of the cohort members never get sick and they don't contribute very much incremental information. So if you can collect information and store it, as in blood, as in DNA, et cetera, you're able then to apply this design, and you can expand it to other types of study concepts.

I think I'll stop here at this point and see if there are questions and go from there.

DR. TUCKSON: Well, thank you very much. Very, very good.

Any hot questions right now? If not, we'll come back.

(No response.)

DR. TUCKSON: Well, thank you for that.

There is a 10-minute break. It is now 10:10. We are going to reassemble at 10:20.

The committee members need to go immediately, and if you have not now gone right out the door, there is a lovely woman there who is taking your food order. If you don't get it in right now, you don't eat, and then you'll be oh so sad.

See you at 10:20.

(Recess.)

DR. TUCKSON: I want to thank everybody for coming back. Thank you all very much.

Our next three presentations will explore the logistical, ethical, legal, and social aspects of large population studies. We are very pleased that Mylene Deschenes has been able to join us on very short notice. It turns out that Bartha Knoppers is in Canada. There is something called a snowstorm up that way. She couldn't get in. So Mylene was very, very kind to come in and help out here.

She will present an overview of the ELSI issues, followed by Charles Rotimi, who will explore the issue of the dichotomy between social identity and ancestry and the ELSI issues raised by this dichotomy. Finally, we will hear from John Newton about the effort to develop the U.K. Biobank.

So with that, let us turn to Mylene to see the ethical, legal, and social issues of large population studies. Thank you so much. As we mentioned, and I don't know if you were here earlier, but there is a little timer there in case you need to time yourself.

DR. DESCHENES: Good morning. Thank you for the opportunity to talk to you about biobanks. As you mentioned, I learned yesterday afternoon that I would be giving this presentation because Bartha's plane was canceled. So I hope that I will be able to convey her ideas, because this is her presentation.

The presentation is divided into three parts. I will first talk about the legal and ethical framework. I think we're still in search of an adequate one, so I will comment on these. I will kind of skip the second part, because I think Teri Manolio earlier on talked a lot about these existing projects. I will focus right around the third part, which are the challenges and issues with respect to population biobanks. I will also talk to you, lastly, about P3G, Public Population Projects in Genomics, at the end of my presentation.

So let's start with a small, brief introduction. I think it is clear now that the way we do research has changed in recent years. We first looked into more single gene disorders, and now we're into more complex

diseases. We are really now focused on national and international collaboration. In fact, they are pivotal to researching complex diseases.

We went from what we call research on traditional biobanks, the small fridge in the researcher's lab, towards human genetic research databases per se. Finally, it's interesting to notice that some issues were at some point considered almost waste. Now they are kind of sacralized to the level of becoming almost equivalent to the person from whom they came.

We should also note that there has been some recent bureaucratization of the ethics review. I don't think the IRB process was initially intended to be maybe as complex and bureaucratized as it is right now, but it is certainly an element we need to take into account.

Human genetic research database. What are we talking about? What is it? For the purpose of this presentation, we'll certainly focus on collection of information that is organized and searchable. It is not just a large bulk of samples. You really need to have a way to search through it.

It is interesting to note that in the legal and ethical literature, oftentimes biobanks, collection, and cohorts are words that are used as if they were all synonyms. We ought to make sure that we use the

appropriate wording.

Also I will focus in this presentation on really the new reality of human genetic research databases, meaning large-scale population databases including at least 10,000 individuals.

So the first section of the presentation, what is the legal and ethical framework, and what struggles do we have in those? I can see two things. First, there is really the trend towards the proliferation and specialization of national and international policies. I will tell you a little bit more about this in a minute.

I think through this we see that this demonstrates the need for harmonization of some of the principle, but most importantly, of the terminology. I will tell you more about this too in a second.

So talking about the proliferation and specialization of law and policy, here you see at the international level within the past three years some of the international guideline legislation or declarations, I should say, that has been adopted by various organizations like HUGO, or the World Health Organization. If you look now at the national level, the title says it all. It is a very uneven playing field. You can see a great disparity between all jurisdictions.

Here you have a few countries that have

implemented legislation that specifically regulates human genetic research databases, and this is very specific legislation. Interestingly enough, the examples we have here all come from the northern part of Europe.

If you look at other jurisdictions, some of them just rely on the current data legislation, public health, and traditional legislation. This really creates some confusion and conflicts, and has overlapped. Some areas are sometimes left even unregulated.

I think this quote from France really says it all. It says, "Several systems co-exist so that the problems are approached from different angles which ignore each other." That's really what can happen. I mean, you try to regulate it by pieces that are maybe not well adapted to the need of human genetic research databases.

However, you can see an increased interest surrounding human genetic research databases. These are just, again, examples of very recent documents that were issued by advisory committees or law reform commissions in various countries. The Canadian Biotechnology Advisory Committee being the most recent one that we have here. So we see that there's an interest and some discomfort at least in the countries with respect to the current situation.

Now, if we go to the second part, the challenge

of our harmonization, I think that at the international level, it is very clear that there is an increased need for harmonization. I think the lack of internationally agreed upon rules, but most importantly, common taxonomy, is really detrimental to research collaboration. It is really an impediment to be able to exchange your sample with other countries, or even just to transfer information. So we need to acknowledge this problem. It is already being acknowledged by various organizations, such as the WHO.

Here you have the Babel tower. Really I think that's how researchers out there feel right now. The Secretary General U.N. quote really says it all. It says, "Despite the existence of numerous declarations, guiding principles, and codes dealing with the issue of genetic data, the changing conditions of genetic research call for the establishment of an international instrument that would enable states to agree on ethical principles, which they would then have to transpose into their legislation." This is really a wish, but I think it is a tool that we really need right now for the type of genetic research that we want to do.

At the national level now, there is a need really to recognize the specificity of human genetic research databases. These are no longer just research projects that you're trying to regulate. These are really

research resources that will be used for multiple future uses. So it's quite the different thing.

There are limits to the traditional consent and personal data privacy legislation. These legislation oftentimes were created again in the context of research for genes for Mendelian diseases, and are not really appropriate in the case of databases like the one that we're talking about here.

There is also a need in personal data and privacy legislation to have a more common language. We know that there is a huge problem with the vocabulary that's being used right now for coded, deanonymized, delinked, and deidentified. And in one country and another country, the same word will mean something different.

So when you want to respect participants and make sure that the consent that follows the sample will really show your partners how they should use the sample, it's a problem. We're not even sure how it is understood between each partner. So there is also a call for the implementation of a more comprehensive regulatory framework so that it will be more easy, I would say, to conduct these types of research.

Well, at least there is some consensus on what we should be working on. The first thing is certainly to work on the tailoring of traditional consent mechanisms to

the specificity of human genetic research databases. Again, we can no longer use the traditional consent models. I don't think it's appropriate, neither for participants, nor for the researchers.

We need to have a better correlation between the degree of data identifiability and all the obligations that comes with it. It is more interesting, of course, to have data that are coded and that we can link to a participant, but it comes with obligation. What are we going to do 20 years from now? Will we have the obligation to bring results to these participants? That's something that we need to clarify.

The need for adequate ethical oversight from the inception of a database, as well as monitoring mechanisms, that is certainly something we need to work on as fast as we can. Initiating, promoting, and strengthening the professional and public dialogue. This is fundamental to the type of enterprise we're talking about. We certainly need to work on it.

It is kind of related to the last point also, the need to develop a benefit sharing policy. We need to do, I think, a better job at really being able to identify the benefits. It's difficult, because we know the benefits are long term. But for the participants, for the funders to be able to justify such an important investment, we need

to be able to have better communication with the public about this.

Some controversial issues. Funding. This is a very sensitive issue. If we want these human genetics research databases to stay in the public domain, the way they will be funded has a tremendous impact. This issue about original consent form and secondary use of sample is also one that is controversial. Are we going to go into this blanket consent? We have very big doubts that that is something that is going to be accepted in the legal system, but it could be possible.

There are suggestions about the authorization model. Maybe it is a new way we should explore. But certainly what is the appropriate type of consent we need here is something we need to further discuss. It is really something that's a sensitive issue, because it will have an impact not only in genetic research, but any other types of research that we're doing out there.

Protecting privacy. Again, the choice of words is very important. Personal feedback. As I said, what are we going to do in large-scale settings. Is it appropriate to think that we're going to be able to bring back individual results? Is this something that is reasonable and feasible?

The status of genetic material. Ownership.

Who owns these databases, the tissue? In certain jurisdictions, the mere fact that you would own tissue is counterintuitive, I would say, and against most basic fundamental principles.

Government structure. Looking into checks and balance is also something I will talk a little bit more about in a second. Ethical review for multi-centered research projects is also quite challenging these days.

I will skip this part and go right through now to the challenges. So if you were to establish a human genetic research database right now, what would you consider? What are the fundamental elements you need to think about?

We think there are at least three elements you'd like to go through. The first one is ensuring legitimacy of your human genetics research database. You'd like to look into the adequate protection, building trust, making sure that it's well protected, and you like to make sure that there are appropriate checks and balances. Let me go into more detail into these three elements.

So if we are looking into legitimacy, as I mentioned earlier, you need to justify putting so much research, money, and resources into these huge human genetics research databases. What are the benefits? How do we need to explain these benefits? So this is key into

the funding and support of the community. We need to work on this, I think.

Legitimacy can come in different ways. In some countries, they have chosen the democratic forum through Parliament and legislation to start these types of human genetic research databases. So here, for example, you have Estonia and Iceland where in these countries, they have adopted the legislation to really create their human genetics research database.

Now, is Parliament the most appropriate way? Or is it the appropriate democratic forum by which you could engage the public and make sure that there is legitimacy there? The question that we had is if there is not enough public consultation, public communication prior to this Parliament enactment of the legislation, we might have questions with respect to the process. But nevertheless, in many countries, at least it is very clear. Whenever there is a legislation, you know the rules, and you know what is being done.

Another project like CARTaGENE, U.K. Biobank, HapMap, and others, the initiative, instead of going through Parliament, is a project that was started by scientists themselves. They are adapting the science to the community's needs and the population's desires through discussion. Again, in this case, it is more, I would say,

self-regulated, but the participants have really again here discussed the regulatory framework that is being built.

So these are two different ways in which you could approach it. Now, for a transnational enterprise, it is a little bit more complex, like GenomeEUtwin, P3G, or HapMap. These are transnational international collaborations. Here, the success really depends on trust and communication between members, and based on common understanding of the issues and agreements on the scientific, ethical, legal, social issues and common philosophy. So this is quite challenging, but at the same time, the benefits are I think incredible.

Now, the second part is about building trust. Building trust at different levels. First, ensuring public representation, and ideally, inclusion of all the groups that could be representing the sample population. But we know that there are financial constraints, and it's not always possible.

Building trust with the community really depends on your communication strategy. We cannot emphasize enough how important it is to really create a communications strategy that will really include the community from the start, and that will really enable bilateral communication, if I should say so.

Ensure data collector's participation and

expertise, making sure that the people that will collect the data are properly trained, and that the researchers also are sensitive to all these ethical, legal, and social issues. That's something you'll want to think about.

Privacy consent issues. Again, privacy is oftentimes the thing that worries I would say, communities. That's the first thing that will come. In a way, it's legitimate, because you are in these human genetic research databases, you're putting in all of this sensitive information, and really concentrating in one spot. So it is legitimate that they have questions, but I think we have to just be able to answer with appropriate tools, choosing an appropriate consent process, looking into our security mechanism, and looking into the types of identifiability of the samples that you are going to look into.

Individual feedback and general results. Again, that is something that the research team will have to make a decision about. You see here different options. In Estonia, they chose to really respect the right to know in a way, and in other projects, there will be no research results except for the medical examination from the start. So that's another element you'll need to consider.

Is it possible? That's the question that we're wondering. Is it even possible in such large-scale projects to get the appropriate genetic counseling to

really make sure that you don't fall into the potential problems in genetic discrimination or misinterpretation of results.

Finally, stigmatization and discrimination are really issues you want to consider in the commercial aspect. This is a very tough one, making sure that you get free public access, yet at the same time, we need to respect all these intellectual property rights that are involved.

The involvement of the industry, I think there is the financial resource needed for these types of projects. Often we will for sure need the involvement of the industry, but how to do it, at what level, and how to appropriately make it, that's the question.

Finally, checks and balance. Thinking about checks and balance, you need to think about it from the start to get approval of not only the protocols that will use your huge human genetic research database, but you need to look into the framework itself. You need to get a stamp of approval.

We learned from the authorities it could be anybody from the ethics community to other types of authorities, making sure that the public is recognized, again, as a true partner, and will have its say in the establishment and creation of the framework itself, and

need to build a mechanism for the review procedure. It needs to be there from the start.

If you look into the research project review and monitoring, this is really I think a quite challenging area. We want to set mechanisms to really make sure that there will be appropriate ongoing monitoring not only of the research project, but again, of these public resources, and how it will be set.

The U.K. Biobank did something very interesting. I think there are very innovative solutions out there, but we need to still work on those.

Finally, the management structures. In each of these projects, they have built interesting charts on how the project would be managed and appropriately balanced. So we need to ensure transparency, independence, and integrity. But to create, conceive, and conceptualize these management structures is quite challenging for researchers as well.

I will go through just before I say it, and talk about the conclusion. I want to talk to you a little bit about the P3G project. I thought through the presentation I have been talking about some of the challenges, the problem of organization, and the problem of having different taxonomy to designate similar things.

Public Population Project in Genomics is a non

for profit organization that is currently building an international consortium to really promote the type of discussion and collaboration that we need in the field of population genetics research. We want to foster this international organization and discussion at all levels.

At the scientific level first to be able, for instance, to have common words to designate the type of research, common ways to collect data, and also at the ethical/legal/social level to make sure that people are provided with the types of tools, and that we can benefit from the experience also of other population genetic research databases that are already out there.

We want ultimately to create a body of knowledge that will be publicly available so that all the human genetic research databases that are out there will have an opportunity to really be able to communicate with each other, to be able to compare data if it is interesting, and to be able to exchange data, because they will have had an advance talk about this organization of taxonomy, and dealt with some of these issues of making sure that we have a common approach and common vocabulary.

The current partners in the P3G project, and I'll just go back in the slides to show you the website if you're interested to know more, the current partners are GenomeEUtwin, the Estonian Genome Project, CARTaGENE, and

CIMGR, which is a Manchester project. We have other partners that are coming up in the project right now. The Chair of the board for this project is Bartha Knoppers. So if you'd like to know a little bit more about P3G, I invite you basically to go see our website.

So just in conclusion, I think we're building really unprecedented, very interesting research tools that will be used for generations to come. But I think the legal and ethical tools right now might not really deal appropriately with all the issues that are raised. I think oftentimes they were created, as I mentioned earlier, for drug research, or Mendelian research. I think if we want these biobanks to really span the test of time, we need to look at three things.

We need to probably revisit the current ethical/legal framework. We certainly need to make sure that participants are on board, and communities are on board very early on in these types of projects. I think ultimately the success of these types of human genetic research databases will rely on their trust in these types of tools.

We have a common goal here. It is really to benefit the health of everybody. I think we then should have common vocabulary, and we still don't have this yet. So we need to work on this.

Thank you very much.

DR. TUCKSON: Thank you very much, Mylene. That was terrific on its own merit, but even more terrific for having stepped in at the last second.

I'm looking forward to Hunt's opportunity to lead the roundtable with all of our participants and the opportunity to query each of you at that time. Let's turn now to Charles Rotimi, who will share his thoughts on the dichotomy between social identity and ancestry in large population studies.

Charles, thank you. Again, Charles is Acting Director of the National Human Genome Center at Howard University.

DR. ROTIMI: Thank you. Thanks for inviting me.

What I thought I would do today is share with you some of my thoughts, some of my biases, and how I think about some of these issues in relation to how we do large population studies, and how we try to represent different groups, or not represent different groups for various reasons.

One of the first comments I wanted to make is that depending on what we are doing, we desire different levels of resolutions. For example, if we are trying to identify how common alleles, at least 5 percent or higher,

impact on disease, we will define our study in such a way that we have a level of resolution to get at that. For example, HapMap.

If we want to identify people who eat beef, that is one level of resolution. If we want to identify people who not only eat beef, but eat it in a certain way, cook it in a certain way, that's another level of resolution, and you may have to go to some parts of the world, and not other parts of the world.

So again, depending on how we are defining ourselves and our identity, we do stop at different parts of this. If you really look in terms of our own history, one can say that we are indeed Africans, and that we started somewhere in terms of the roots and trunk of human evolutionary history from somewhere in Africa.

But of course time did not stop, and we are migrating to different parts of the world. Depending on your socialization, and depending on what you are willing to accept, how you want to define yourself, and indeed sometimes it is the question of survival, the identity you want to put forward. Your level of resolutions do differ, and we have to always bring that to bear.

That is why it is extremely important when we are defining large-scale studies like what we are planning here, that is capable of impacting on health for a very

long time, we need to be extremely careful as to who is at the table, and who is making decisions.

Not just in terms of science, but in terms of how is this representing the people. Especially if you are using taxpayer's money. So again, it is extremely important for us to appreciate all of that. And indeed scientists were socialized before they became scientists. We bring all of our baggage to these issues.

Also I want to again, make some distinction here. That is in terms of when we are talking about understanding etiology, and when we are talking about eliminating her disparity. Sometimes we say these things and say they are the same, and sometimes there is overlap. I actually wanted to make this overlap a little bigger, but I couldn't figure it out in the PowerPoint.

It is indeed a little bigger than that, but there is not a complete overlap. For example, if you are interested in eliminating her disparity, you may be interested in how people get access to care. That may have nothing to do in terms of etiology. So again, we need to be clear as to what is it that we want to do.

Looking at her disparity may have more involvement in strategy at a social level. Again, typically we look at a diagram like this, and we usually use this to represent her disparity, and sometimes to point

out etiology.

One of the things I wanted to point out here is when you look at a 50 percent prevalence of Type 2 diabetes among Pima Indians, one has to wonder within the same United States as to what is going on. The gene hasn't changed that much. It doesn't mean genetics is not involved, but it hasn't changed that much over the years.

One of the things that we do know is that characteristics have changed. So again, looking at this, you can be looking at etiology, you can be looking at her disparity, and at the same time, you may be addressing both.

Now, this is on account of her disparity. This is looking at populations of the African diaspora. Again, this is where I used to stay when I was working at Loyola Medical Center in Chicago. It is 84 percent African American. This whole cohort here is over 10,000 people from different parts of the diaspora.

What you do see, again, is that this is clearly her disparity issue among people who have African ancestry. About 14 percent here, about 34 percent here. You do see a dramatic increase in body mass index. So clearly how heavy you are and the environment where you find yourself has serious implications for hypertension.

This is a new study that is extremely important

in terms of how we address some of these issues, what we are calling disparity, and how it plays out in different ethnic groups in different parts of this continuum in terms of human experience with the problem of hypertension. This was done with Richard Cooper and his colleagues recently.

What did you see? Again, clearly depending on where you are, you do have very different rates. What I want to point out here, when you look at whites, the group we called whites within the United States in relation to other ethnic groups, typically we see it as a huge disparity.

Yes, there is a huge disparity, but if you place all of these populations and you look at it together, you see that it is truly a human experience. When you are in Germany, your rate of hypertension is really, really high. The U.S. whites tend to be quite healthy in relation to other European populations.

Therefore, it exaggerates, to a large extent, how we think about the issue of who is getting hypertension, and who is not. So again, this slide here is really important when we are doing a large-scale cohorts like this, that we have to bring to bear cross-culturalized and international experiences, so that when we are defining our variables and strategy, that we take those into consideration.

This is the same sort of study. Now, if you group all of your opinions, the populations and all African populations, you do see that the Europeans have a much higher level of diastolic blood pressure. But you don't hear this when you hear people talking about experiences of high blood pressure and hypertension. So again, cross-cultural comparisons are extremely important, and international experience is extremely important in doing these large-scale studies.

Also, in what we want these large-scale studies to answer, we also have to define this study. Do we want it to just stop at a level of who gets diabetes, yes/no? Who is reacting to drugs, yes/no? Or are we also wanting to tell some stories about who we are, where we are from, and are we related. It may be useful. If indeed it is, then we need to bring to bear a design strategy that will help us to see those things in the way that we are not reinforcing old notions about who we are. So in that regard, ancestry, in my opinion, becomes a very critical thing for us to consider.

I like these slides a lot, because every time people talk about the issue of race/ethnicity, I am getting so tired of the whole issue, but I always ask myself, where do we draw boundaries, and how do we draw boundaries? Again, it really just depends on where you grew up, how you

were socialized, the things that you are afraid of, and the things that you like.

So who is black? This is a whole spectrum of who is black. This spectrum is indeed also limited. You can expand this. There is no limit to it.

One of the best pictures I have seen so far is on the PBS website where they actually show that you can see all the variations of human complexion right there in Africa. All of it. I'll show you some of my experiences when I was in Brazil. I'll tell you a story in a minute. But you do see that these all would be considered black. But again, they have a radically different ancestral history from the Aborigines, to Ethiopia, and different parts of the world.

I put this slide here to tell a story about what we are doing in terms of Type 2 diabetes in the African diaspora. This is a study we are doing in Nigeria and Ghana, but the real intention here, what we are trying to get at, is why the high rate of Type 2 diabetes in African Americans.

We felt compelled to really get at that. We need to go back to the source population of African Americans. We all know the ugly history of the Middle Passage, and that most African Americans, again, came from this part of West Africa, and again, Mozambique.

The story here I really want to point out is when we started writing the manuscript reporting the results of this study, one of the things that reviewers took us to task on is how you are sure that you can combine all of these groups together, because these are an affected pair design.

We analyzed the cohort. There were about 400 affected pairs with Type 2 diabetes. We analyzed this cohort as a uniform group, as one group. But repeatedly the reviewers gave us trouble and said, why do you think you can combine all of these groups together?

But the point here is that I have done similar work in African Americans, and no reviewer has taken me to task that why do I think African Americans are a uniform group? You see the way we are socialized impacts even on the way we review the work and what we fund, because indeed, this kind of work, if you are writing a grant, it can be killed based on that reason only, that reasoning, but you know that even the ancestral history of African Americans is even broader than what we have here. But nobody takes us to task on it, because the assumption is we are dealing with a uniform, homogeneous group.

So we need to be very conscious about what we're talking about. The problem I see is that group identity is confused with ancestry, and self-identification

is confused with more complex ancestry.

Now, when I prepared the slides for this talk, I wondered about this issue. But if you think the issue of African Americans is confusing, not to talk about the history of the Hispanic population, or what we would call Hispanic, that is completely mindblowing when you look at it where we classify who we put under that umbrella. How we approach it, with some notion of uniformity, to me really begs the question of what are we doing.

It may indicate why we are not getting some consistent results in some of the work that we've been doing, because we lump people together based on some very interesting groupings.

For example, when we look at the Census, the Census is pretty clear. I think this is one of the issues that confuses it. We say we're not doing anything that deals with biology, we are just looking at it where society has designed itself, and we are collecting information on that. But what we do as scientists, we impose biology on that, or want to impose biology on that. Sometimes it works, sometimes it doesn't work. So I say Hispanic, but you can be of any race.

So this is just to point out some of the groups we call Hispanic. Mexican, South America, Cuba, Puerto Rico. This is a whole list of people who have radically

different ancestry if you really go into the history.

I put a slide here. I took this picture on my last and only visit so far to Rio. It was friendly and informative for me, and I enjoyed myself quite a bit.

I was flabbergasted when I drove on a major road going to the university in Rio, and I saw this junction. It took me back to my young elementary school days when I was in Nigeria going to school. We used to put our school bag -- ours was made out of a metal box, and we put them in on our heads. We were so good, we could play soccer on the way to school.

But what it turns out is that this is a sacrifice made to the Gods in Rio, and it followed the tradition. I was extremely surprised by that. What you have is these are the feathers of a chicken, pots, oil, and wine, making offerings to the God for protection.

This is three years ago in Rio. Now, talk about gene/environment interaction. If you are studying this group, then you had better take into consideration the African ancestry and history, and why this group has kept this experience over the years. What does it mean, therefore, to have Cuba, Mexico, and Brazil as Hispanic in studying the group?

This is, again, to show you again how we lump people and sometimes lose quite a bit of information. If

you look at people who are under 18 and 65 plus, you do see that depending on which population, the Hispanic population that we are sampling, you could be doing yourself a service or a disservice.

The same thing also here in terms of education. There are radically different education experiences.

I think the same story is true when we look at Asians. We do group all of these groups, and we call it Asian. Now, for example, HapMap is looking at Japanese and Chinese. Now, how does that represent the experiences of these people and the ancestral history of these people. And if indeed there is something that has been selected over the years and these are the only experiences, it may indeed not be well captured. I don't know. But again, for us to just be conscious of who we are calling Asians.

One of the other extremes in this experience in working, and actually I live in the United States, is that depending on how you see yourself and how you relate to your environment, you tend to lose some of the social identity that you have. It's not important anymore to be German American. It doesn't offer you any extra advantage, okay? Whereas it may be extremely important for you to identify yourself as Native American, or Hispanic, or however it is you want to do it.

But again, this shows that depending on the

group, who is sitting at the table, they might see the relevance of setting things and not the relevance of all this. So we need to begin to be very careful as to why we are using this and how this came about, and what is their present relevance.

Now, to sort of wrap up here, looking at ethnicity identity in terms of Africa. One of the things that has happened over the years, and this is just one of the issues I take with cultural anthropologists, and I tend to single them out, but they are not the only guilty one.

It is this whole notion of things which end up in part of the world, or in a remote environment, sort of static and that they don't change, or that we don't want them to change. So if people are cooking in one particular way, we want them to continue to cook, whereas in our environment, we are creating jets that can carry 800 people now and things like that. We are lots of society to evolve, and one part is to stay static.

I don't know the rationale behind that, but the point is that just like anywhere in the world, identity changes. How we look at ourselves changes. Those things have been based on economic, political, and whatever else ways for us, especially the issue of survival.

I would say that we are extremely efficient in the way we identify differences, because I do believe

somewhere down the road that we need it to be so. We need it to be known who is family, who is friend, and who is outside of that cycle. So we are very, very good at seeing differences that may not actually be the reality.

So the message here really is that things have not remained static, that identity changes. It is multi-layered. Depending on where you are looking, genetics may be important, and they may not be. Making the sacrifice at the junction on the road may be more relevant in terms of the issue.

So I'd like to end by just again bringing us to some areas in terms of who is telling the story. Depending on who is telling the story, depending on who is designing the study, depending on who is present, who is funding this study, you can tell stories and history in a very, very different way.

For example, during the earlier interactions between Europeans and Africans, there were some various surprises that were not anticipated, and because of the biases that came or preconceived notions, certain things were very difficult to assert.

By the way, this is where I grew up. So I know this history quite well, and some of the issues that we have, again, we are still trying to get some of the artwork that went away a long time ago.

But the take-home message here for this particular slide is that we need to think more comprehensively if we are going to design very large studies, especially if we are going after gene/environment interactions.

Again, this is the same set of points. I'm just going to skip these.

But where do we sample? Again, it becomes very, very relevant. Very interestingly, only European Americans, again, that's a very broad term, no question who is under that umbrella. You can sample anywhere in the United States for that group.

But if you are interested in American Indians, Eskimos, Asians, blacks, or Hispanics, you have to go to different parts of the United States. For example, you do see most African Americans here. The people we would call Hispanics are here.

So again, it is very, very important if you want to emphasize efficiency that you go, and depending on also who you are putting under that umbrella of Hispanic, it may do you better to be in Florida and to be in California. Again, just for us to be conscious of that.

This is something that we did recently at Howard University with Nature Genetics and some of the people that are here who actually contributed to that

effort.

It is really to try to get at how do we explain the fact that, yes, there is variation at the genome level, and that variation needs to be studied. How do we do it in such a way that we don't bring our whole notions on it? Let it tell its own story so we can really know how we are related.

But the point I also want to make with this slide is depending on where you draw circles here, here, or here, the genetic variation will tell you a story. If you move, it will tell you a story. There will be overlap. There might be some differential frequency. But usually what happens is you don't have uniqueness. It is just a gradation.

So in terms of large scale, I look at large scale as this big umbrella, and that we are trying to fit a lot of things under this big umbrella. Depending on how many things we want to fit under this umbrella, it would determine the level of compromise that we are going to have to make. This could be prostate cancer, heart disease, or something within heart disease. Again, this could be infectious diseases, HIV, whatever.

So depending on what are the things that we want to put under this umbrella, we are going to compromise. We are going to have to make some compromises.

I want to say at this point that the really critical thing here is the cost of phenotyping that is going to drive all of this effort.

At some point in the very near future, five years or so down the road, we are probably going to have all of our genetic variants on a chip and put it on our neck like an I.D. card.

But the environment is interesting, because it is everchanging on us, and it would depend on how we feel today. My blood pressure can be high or it can be low. Just looking at you, I can be smiling, and things are happening to my physiology. How do we capture that in a way that we can relate it to genes that are supposed to be under the influence of this environment? I think we need to think carefully how many things we want to put under this umbrella, and what we want it to answer.

So as the final note here, the whole point I'm trying to make in my presentation, or tried to make, was this point here. "The historical, anthropological, and linguistic definition of populations, within which genetic finders are correlated to represent superficial understanding of the dynamic history of presenting ethnic populations or high-risk populations were developed."

The future use of drug therapy will not depend on the (inaudible) race/ethnicity, but on the individual

patient. I think David Goldstein made this point earlier. The idea then is not to eradicate or ignore differences, but to redefine or move beyond social group labels such as (inaudible) to more precise categories of differences with justification for establishing such differences.

Thank you very much.

DR. TUCKSON: Thank you very much as well. We very much appreciated that. Thank you.

Now let me invite John Newton from the U.K. Biobank to share his perspectives. You've come a long way, so thank you.

DR. NEWTON: Thank you very much, Mr. Chairman, for inviting me. It has been very interesting listening to the previous speakers, and it is a pleasure to be here to tell you more about the U.K. Biobank.

The first thing to say is actually what a superb job the previous speakers have done of giving you a background to these issues. They saved me a great deal of trouble, and I think they've educated you a lot.

I think what I'd like to do is make a few general points, and then move on to really tell you more about the U.K. Biobank and the project itself, so you have a clear idea of what we're doing, how far we've gotten, and what it all might mean for things that you're considering as well.

So as Gil has already told you very well, U.K. Biobank is a project, it is not a single study. It is infrastructure. The aim is to support a whole range of studies, a range which we cannot really define now, in which we cannot define partly because they will be answering sheets of questions which we haven't yet phrased.

So it is a project to support a large number of studies with the overall objective of a better understanding of the way genes and environment work separately and together to influence health and illness. We are choosing to look at a large group. In our case, we define large as 500,000 participants.

I think what we've all agreed on is that the last decade of the last century saw biomedical science transformed by the Human Genome Project.

This is John Solstum from Cambridge. He had a role alongside many international colleagues in the Human Genome Project.

The Human Genome Project is truly staggering. But there is a danger that the project will become the museum exhibit of the 21st Century. I think it presents two challenges. There is a technical challenge. How do we take the human genome and work with that to produce science which is broader than simply sequencing the genome?

But there is also I think a moral and political

challenge. How do we capitalize on that enormous breakthrough in science in terms of wider benefits to society and to public health in particular?

You could talk about going from the hype to the history. I think people will look back at this decade and say well, what did they do? They had the Human Genome Project, what did they do with it? The sort of things that they will look at are things like the HapMap, which I agree is an excellent project. We have to think, what else is there? We should be asking big questions now about what people will want in 10, 20, 30 years time.

Someone else said this is rather like planting the shade trees for the future. You have to think forward, particularly if you're talking about prospective studies. They take 10 to 20 years for the real fruit to be borne. Because they have a long lead time, it in fact makes them very urgent. It means we must start them urgently. Otherwise, we'll have to wait even longer for the results.

But I also agree with David that there is a very important job to be done now. It is urgent, but we mustn't rush it. The detail work that we do now will determine the quality, the value, the comprehensiveness, and the scope of the results that people have in the future.

So what we have to do in the challenges to make

sense of the data, we need to turn the data into information, and into knowledge. People like Sydney Brenner have come to epidemiology perhaps slightly late in his life, and has made this point very well. We need to start thinking not just about a genome, but about the distribution of genomes, distribution of genetic factors in the population, and what it really means for us all.

So to summarize, maybe in the 20th Century we had some discrete questions which we have answered I think very effectively. Things like the classic epidemiological questions of smoking, lung cancer, and other issues that perhaps we haven't tackled quite so clearly, and we have the genome sequences. We have very clear results from some of the biomedical sciences.

But we have to try and compile those together into meaningful 21st Century questions. I have just had a go, but one of them might be which HRT users will develop breast cancer and why, and you will have many others. I mean, as I said before, the questions are not known now, but they will arise.

I agree also with Gil, that many of these will relate to environment. Clearly nowadays we are much more interested in packs of smoking rather than individual smoking. We need to think. We need to be innovative. If we are merely contemporary now, then these prospective

studies will be out of date. We have to think innovatively now in order to be contemporary in the future.

Now, one of the things that you quickly get to when you start thinking about these questions is that the ideas of the size of current studies are too small, that you need very large studies. As Henry Ford said, "Quantity has a quality all of its own" in epidemiology, as in manufacturing.

This is part of a general trend in epidemiology and clinical trials. These are just some of the studies in the U.K. showing how many people were recruited, from 20,000 up to 120,000. So there is a general trend to recruit more and more people at baseline. In the U.K., we have the million women study which successfully recruited in fact, at one point, 2 million people. They overshot, they tried to stop at about 900,000, and ended up with 1.2 million.

So there are a number of things to learn from this. Firstly, there is nothing that we are trying to do with the U.K. Biobank that hasn't been done before by people in different studies, albeit on a smaller scale.

But the second thing is that these very big studies are feasible. They are difficult, they present challenges, but they are feasible. The public responds very well to them. I agree, again, with the previous

speaker, that the public can identify with these problems, and the solutions to those problems. They know that we don't know all the answers, and they would like to help us to get the answer.

So what is Biobank? You've heard a quick sketch, and I'll try to just fill in a bit more detail, but perhaps take questions on further elements of detail later.

We are starting with 500,000 people. We have changed our age range. We have gone down to age 40 to 69 for reasons which I could explain. The essential idea is relatively simple. We identified volunteers at baseline. We collect information on environmental exposures, we take certain measurements from them, they fill in a questionnaire, and then we take biological samples, blood and urine. We've considered various other samples, and we settled on blood and urine.

We then tracked those participants, taking advantage of the benefits of the U.K.'s National Health Service, corporation registration, and universal health care coverage, which gives us a very good start, but not all the data that we need. By no means all the data will come from these routine sources, but they are an extremely good screen from which to undertake additional validation exercises, including perhaps questionnaires in the future and recontact for validation.

I should perhaps say at this point by the way that we have taken the issue of environmental exposures very seriously. There is a subgroup set up on our Science Committee which is considering these. We have taken advice from the Health Protection Agency in the U.K., and environmental epidemiologists such as David Coggin are advising us on that.

The general point is that there is a lot of detail work going on on exactly how to measure exposures at baseline, which is being brought together by a number of subgroups advising our Science Committee. We plan to publish the results of that we hope by April of this year and invite comment, as we have done for all the other pieces of work that we've done. For example, the ethics and governments framework. So I hope that people in the United States will contribute to the process.

So here is the U.K. population in 2001. That's the U.K. Biobank corporation. You can see that the reason for choosing this age group is that there are broadly the same number of people in each age group here. This is the beginning of the slippery slope, I'm afraid, for most of us who were just in there. The major causes of death and morbidity start to kick in. I'm afraid from here on in, it is incidents of major disease outcomes. Of course, that's the point at which these studies start to be interesting.

There is an issue of how far back can you ascertain exposures. Some people argue, well, you really should be starting down here. You start with the children, because that's where the seeds of illness are sewn. We can debate the pros and cons of these. There is no answer to this. We need studies of children, and people are starting studies of children. We need studies of adults. We probably need studies of the elderly as well.

So it is important not to oversell these projects. Biobank is a big project, but it is only one part of a strategy to answer these questions.

It is a big study. There are lots of people in there who will develop lots of conditions, unfortunately. This is just to give you a flavor of the numbers. At baseline, within five years, we will have people with these sorts of numbers of conditions. So 8,000 people will have coronary heart disease. At the time, 7,000 will be diabetic, and 1.6 will have Parkinson's, and this is rheumatoid arthritis.

Now, these assumptions take advantage of what we know about volunteer bias. So quite a lot of work has gone into these estimates. We feel they are quite reliable. Importantly, there will be large numbers of people at baseline who suffer from various risk factors for disease as well. Therefore, we study the effect they have

on people's health as they get older.

There are similar numbers for the numbers of people who would develop instant illness in the future. Gil talked about ten years. In fact, we plan to study people indefinitely. So we are talking now about 10, 20, 30 years. At 20 years, we will have 86,000 people who have developed coronary heart disease who didn't have it at baseline. These are the sorts of numbers that you need if you're really going to get to grips with the interesting questions.

Scientific objectives. Very broad categories, but starting off with the public health aim which is to determine these separate and combined effects of genes and environment, and the nested case-control studies which you have heard about is really the selling point to the Biobank.

That was the one that really convinced the scientific peer reviewers that Biobank was worth doing. But nevertheless, you can also do cross-sectional prevalence studies, because there will be large numbers of people with diseases. If you choose the right diseases, for example, things like cirrhosis, you can do really rather nice studies on the cross-sectional studies on the prevalent cases, whereas with other conditions, you require instant cases.

We can also do cohort studies, the classic cohort studies looking at the particular exposure. Maybe an environmental exposure, or perhaps exposure to pesticides or some other condition, passive smoking, social class, or some occupational factor, and follow them up as a group.

An interesting variant on the exposure-based studies is genotype driven clinical investigation. We are recruiting a half million people, and there is every expectation that perhaps within five years it will be possible to genotype the whole cohort for at least a limited number of SNPs. It will then be possible to identify people with certain SNPs and invite them so they could volunteer in an appropriate fashion to take part in studies looking at the effect of those genotypes in the representative group of people, as opposed to people who you have identified because they are ill.

It is potentially very powerful. It raises a whole new set of ethical and legal problems even on top of the ones that Mylene described, I think. But nevertheless, we have had some quite interesting discussions with the relevant groups in the U.K. suggesting that this is likely to be feasible, provided it is done carefully.

The third big area of interest of course is in identifying biomarkers as early risk factors. Not just as

a potential diagnostic tool, but it is something which helps us to explain the model, the fact that the substance is raised before someone has developed the disease may give clues to the disease mechanism.

In general, I think the point about this is that studies like Biobank and all the other studies we've talked about, and indeed comprehensive studies, will help us to understand disease models in a way that we never have done before. That of course is really the Holy grail of biomedical research. What we do with it is a separate question.

Particular scientific justification for prospective studies. Again, you've heard this before. Just perhaps one or two things. Having genetic information on people, regardless of severity, is important. If you take coronary heart disease, many of the people who develop coronary heart disease, it arises as sudden death. Not having samples beforehand can be a problem, or indeed risk factors beforehand.

Again, ascertaining blood samples, generally particularly for proteomics, not just for genetics, is very important. A general point about genetic studies is that if you take genes as just another risk factor, it is very important that, perhaps as Charles pointed out, you have to have no preconceptions about what the disease risk factor

relationships might be.

If you start with case-control studies, you will very rarely detect relationships with diseases that you hadn't thought of. So if a particular gene causes Parkinson's rather than breast cancer, if you are doing a case-control study of breast cancer, you won't detect that relationship. So it's important to be able to pick up things which you weren't expecting.

It is important, finally, to be able to study health, as well as disease. I would argue that you can only really do that by taking samples of the whole population, not just a group of apparently representative cases and controls.

So to recap, the general benefits of U.K. Biobank lie in public health and looking at how these factors work together in populations, clinical medicine, understanding disease groups better, particularly looking at heterogeneity, 21st Century diagnosis, 21st Century prognosis as the essence of good clinical medicine, and bioscience. Particularly the biomarker disease associations.

The process of doing Biobank raises a whole lot of issues that we have had to work through. We think that will have some benefits for others, particularly our work on ethics and governments. The whole approach tends to

provide better access to resources for scientists, and it promotes international collaboration. In some senses, it is efficient and economically beneficial as well.

Moving really onto the detail of Biobank itself. How is the U.K. Biobank funded? Well, these four research funders came together. The total cost of Biobank is 61 million pounds, about $110 million, of which the lion's share comes in the Medical Research Council and the Wellcome Trust, the Wellcome Trust being a large biomedical research charity, as well as the government, Department of Health, and Scottish Executive.

Is that a lot of money? It is approximately the cost of a Hollywood film. "Terminator 3" cost the same as Biobank. Some would argue that "Terminator 3" made a profit. Biobank may make a profit, too.

(Laughter.)

DR. NEWTON: Of course, the point there is that the value statement for Biobank is that the value of the resources is worth a lot more than the cost of collecting it. That becomes increasingly true as time goes on.

Another statistic, the health service in the U.K. spends the same amount in eight hours. So if we can have some benefit on health care, it will seem a small amount of money. Again, another comparative cost. The cost of Biobank is about 1 percent of that spent on

biomedical research in the U.K. So funding a project like Biobank isn't really distorting funding priorities in the U.K. That's my bit on the funding.

How have we established Biobank? Well, it is important to do this properly. It seems like very hard work, but I'm sure it has been worthwhile. We have a board, Biobank itself is a company, a charity with charitable aims, but an independent company.

There is a separate Science Committee which advises Biobank on all matters scientific. There is on the other side, a separate Ethics and Governance Council which is independent, chaired by a Professor of Bioethics which advises Biobank on ethics and governance, particularly in relation to the interested participants. We'll continue to advise Biobank, and we'll speak publicly about whether Biobank is conforming to its ethics and governance policies.

In terms of implementation, we have six regional collaborating centers which represent scientific groups around the country, comprising 22 universities in all.

The general approach is to try to be as efficient as possible. This is a very large-scale process. If we're not efficient, we will fail. It is very easy to spend 61 million pounds and not deliver Biobank. I think

it is possible to spend 61 million pounds and deliver Biobank.

It is an industrial scale process. I would emphasize the need for process and project planning early on. We've done a lot of that.

A distributed scientific collaboration is, I think, the only way to do this. But you do have to have strong central coordination. There is a potential to build a Tower of Babel in producing these big projects. There is a fine line to be cut between having masses and masses of talk and no action, and enough talk to make sure that you've covered all the bases you need to cover.

We particularly value the international collaborations. We've had a number of meetings with people in the United States which have all helped a lot. We do send out our material for comment quite widely. Again, we very much appreciate the comments that we receive.

So we will recruit participants. We recruit in the skill set from primary care, although in fact we are probably not going to use practices themselves that much. Essentially recruiting to the Biobank is rather like launching a new mobile phone. You've got to try to with direct mailing attract half a million people to in essence buy into your idea. So after considerable thought and planning, we are probably going to take more of that sort

of line.

So we are going to start off relatively small and try and get the procedures absolutely right in the first year, and then roll it out in a mass way, taking into account this experience that you tend to overshoot in the end if you don't stop early.

How will participants enter Biobank? Well, they will attend the clinic. We have set up a dedicated clinic to do the data collection. Again, the efficiency of this process is so important that we think dedicated clinics are the only way to do it.

Samples are transported to a central resource, along with the data. The questions we hope will be on tox screen entry so that the data will instantly be amalgamated into the central resource as soon as the participants enter it. There's a big emphasis on archiving and curating the samples and the data for long-term use.

Of course, box number five is very important. It is always easy to forget this. In the end, the resource is only as good as the extent to which you can distribute and make available the data and the samples for future use. It is important to put resources into that now as well.

Data management is a big challenge. I'll just flip through this relatively quickly. We've got a lot of data acquired at recruitment to deal with the

questionnaire, the samples, how the samples are stored, and the quality assurance data. At the end, we have information coming in from the NHS particularly, but also research input as well from dedicated follow-up procedures. The whole lot has to be amalgamated in a secure database.

There is also a lot of IT around the booking, scheduling, the managing of the process. All of this is new, and it has got to be developed. There is a lot of interest from the commercial suppliers, and we are working with some of them to develop these systems. Although mostly it is the experience of researchers that really tells you what is going to happen.

We also have a big investment in the U.K. in the National Program for IT. Many billions of pounds are being spent on drawing together these data sources, which may or may not be useful for us. We're not dependent upon them, but they would help.

Samples. Samples I mentioned earlier. We have done a lot of work on this. It was an expert group that pondered this, reviewed the literature, and produced a report which is available on the Web. We sent it out for peer review. In the end, we decided this is what we're going to do. We will get things rolling, but we think the mistakes we've made will be pardonable in the future because of the way we approached it.

In essence, we are collecting blood in various different ways so that they can be made available for the things that scientists want to do. Say there is going to be plasma and serum. We can do baseline hematology and baseline biochemistry. But the key to it is storing blood in such a way that people can do genetic, proteomic, and metabolic studies, as well as urine, particularly for metabolic studies. We also store blood, whole blood, so that we can immortalize white cells in the future, if necessary.

I just want to emphasize the volume of work involved, at peak we will be recruiting 750 people a day. That's some 3,750 bottles arriving in the lab every day. The storage will generate 24 million tubes, each of which are identified with two additional markers. This is a huge, huge resource, and it is quite a challenge to manage it.

The tubes we have stored in two ways. Traditional liquid nitrogen. You probably need that for whole blood in order to be able to immortalize white cells at that very low temperature. Putting blood into these things is fine. Getting them out is a lot more difficult. Traditionally, people have used liquid nitrogen storage facilities, and they are secure, so we will do that. But we also use an automated -80 storage.

This is a system where the tubes, you'll see in a moment, are stored in racks in here. These are held at -80 degrees. The robot operates at -20 degrees. This is a mock working factory, but it is very similar to the one that will be built in our storage facility.

The robot then essentially processes all the samples according to protocols, which are computerized. It uses a laser to recognize the tube markers. It knows exactly which tube it is handling all the time. They are extremely efficient. They are used quite widely in the pharmaceutical industry. They are used everywhere really, including restaurants who apparently have them for picking bottles of wine from their cellars. So if it is good enough for them, it is good enough for us.

Of course, the huge advantage is that you can set the thing running, according to the protocol that the scientist has defined. It can issue up to 4,000 samples a day, which can then be made available to research laboratories for analysis. Whereas to extract tubes by hand from liquid nitrogen, it can take up to two months to get 4,000 to 6,000 samples out. That's one person working for two months. It is extremely unpleasant work, if anyone has ever had the experience of doing it. There are health and safety issues.

So this is the way to go, this is the way to do

things in the future. It is cost-effective on the sort of scale that we're doing. The cost of the -80 storage is about the same as the cost of the liquid nitrogen storage.

Ethics and governance. There is a huge amount that I could say about this. To summarize very briefly, Biobank is based on the fact that people are volunteers, and most important, that they can withdraw at any time. They give broad consent to future use, and this is a huge issue. I think I'd be more optimistic. I think broad consent has been quite widely accepted, particularly in Europe, as an essential approach to prospective research.

Now, the question of what broad consent means, and what safeguards you have to put in place to allow broad consent to be reasonable is a big issue, and needs careful consideration.

Data security and confidentiality have to be assured. There is a lot of work that has to be done on this. We have chosen to retain control of the samples. We think people are wary of their DNA being widely distributed, and therefore, we have tight control over the samples. But on the other hand, we have full access to evaluations and tests of the samples and the data for appropriate purposes.

Now, the word "appropriate" needs to be defined, so we have internal and external reviews of the

science and ethics of potential uses at Biobank. One of the safeguards that covers a lot of this is our Independent Ethics and Governance Council, which volunteers -- we undertook a lot of public consultation before we started and drew this up. That was one of the issues that came out of that public consultation that people felt an independent group who could speak on their behalf was important.

We have also had a lot of support from Parliamentarians. We have done a lot of public affairs work with the Science and Technology Advisory Committees for the House of Lords, and for the House of Commons. In fact, there is a very big report from the House of Lords on genetic databases which was done I think as early as 2001, actually.

Biobank is a big study, 500,000, but it's not big enough, by no means. You quickly run out of individuals for a lot of studies. It is essential that we can collaborate. Collaboration means two things. It means encouraging people to set up similar studies and working with them, but it also means harmonization. It is no good if we all did studies which don't talk to each other, which is why the work at P3G is so important, and indeed the work of Muin Khoury's group from CDC, which looks at the other end of looking at the outcome of the research studies.

So there we are in the U.K. These population

studies lend themselves to countries where you have population registration and universal health care coverage. So there is a natural tendency for countries like Canada, U.K., and the Scandinavian countries to think of setting up these studies.

But as we've heard today, there is work going on in Japan, and there is work going on in Singapore. I was at a meeting in Sweden last week with a number of delegates from Singapore. We are very much hoping that the U.S. will make a contribution. Already there are studies such as the Marshfield study, which clearly will make a contribution. I would be astonished if the U.S. doesn't really make an important contribution to this worldwide collaboration.

Of course, you are very welcome to use our data. It would be great if we could swap.

How far have we gotten? Well, here is the timeline. We are starting pilot studies, we are doing some molecular pilot studies testing the sample handling procedures, and testing the clinical procedures. We'll start integrated pilot studies which will look very much like the real study in September of this year. We start the main study in January, 2006. From then on, it is one person every five minutes for five years.

What are we doing at the moment? While we are

looking so tired, it is very hard work. I have to say, it is very hard work setting up these big studies. There is a lot to do.

We are doing the piloting, we are setting up the IT infrastructure, and trying to design the clinical applications. The tox screen questionnaires are quite innovative. Very importantly, we are planning how we approach the general public, and developing a communications strategy to support recruitment.

The participants are fundamental to the studies. If you don't have the trust of the participants, if you don't convey the fact that we think that they are participants, not subjects, then people will walk away from us. So we take this very seriously.

We are developing this under the protocol. The protocol, which was published about two years ago, was really a proposal. There is a huge amount of detail work to be put into the protocol. For example, we mentioned environmental exposure measures. That in itself has produced a wonderful draft report, and there will be a second report. So there is a lot of scientific detail work to be done.

The Ethics and Governance framework will probably remain in draft throughout the project, because it needs to be brought up to date continually. We are

thinking we will produce a new version quite soon. We put it out for public consultation. We are implementing the laboratory processes. We have commissioned our robots, and the people in Cambridge are building the robots. We are building the building.

This is where the automated storage facility is going to be. This is the new headquarters of Greater Manchester Police. This is in Manchester, U.K. So we thought this might be quite good in terms of putting burglars off, to be quite so close to them. These buildings will go up quite quickly. So we hope to have that ready by September of this year.

So what are the challenges? A number of challenges. Delivery against the timelines. It is a big super tanker of projects. It has got many, many people involved, some of whom have vested interests. It's important to try and draw these together behind a common goal.

The ethical approvals. We think we feel secure. We've had a lot of discussions. We think we have a lot of support. We have talked to all the right people. We have been absolutely straightforward about it, but it takes time. It is very difficult to bank on when you're going to get the final approval. So whilst you have your detailed project plan, the ethics committees can feature

quite high in the risk management of that.

We need to negotiate access to all the information sources that we need, and we need to ensure continuity of the data chain over many years. By the time the people come to use the data, we'll all be long gone, so it needs to be carefully documented. Professionally, I should say, long gone.

So finally, what is special about U.K. Biobank that perhaps marks it out? Well, certainly the size of the project. At the moment, I think it is the biggest funded project, both in terms of number of people, but also in the long-term nature of it.

The biological resource will be unprecedented. There was a great deal of interest just in the biomarker. So people would fund Biobank just to get hold of the blood samples. But Biobank is a lot, lot more than that. The epidemiological design of Biobank is what really makes those blood samples valuable. Because the inferences that you draw from the analyses we think will be more reliable than inferences drawn from other biological resources.

We have, in terms of ethics and governance, an important element. We can recall the individuals, the participants, for intensive phenotyping, and for other information gathering exercises. So it is a continuing relationship with them. We are using written records

extensively in the NHS, and we think that that will have quite wide benefits.

I think, again, to emphasize the ethical approach is one of public participation. We hope that by showing that this is an effective approach, that it will to some extent set new standards for this sort of work. Not just in the U.K., but internationally.

Thank you very much.

DR. TUCKSON: Thank you very much.

Kevin, you had one quick question? We'll just do this one, and then we'll go to the next panel.

DR. FITZGERALD: Yes, thank you.

Just a quick question. You keep talking about the public participation, and the participants, not subjects. Do you have outlined a process for how these participants will participate in the process?

DR. NEWTON: In terms of influencing decisionmaking and the managing of the project?

DR. FITZGERALD: Right.

DR. NEWTON: Well, we have a participants panel, and we have been consulting with them in general.

DR. FITZGERALD: Okay.

DR. NEWTON: We have representatives of the public on our Ethics and Governance Council. What we've avoided is a sort of token member of the public on the

board, for example. So I think we're open to ideas, particularly from our panel about that.

DR. FITZGERALD: Thank you.

DR. TUCKSON: Thank you so much, John. I appreciate it.

Now let us move to our next panel, which will inform us about federal programmatic efforts in this area and provide federal perspective on the need for a large population study. In this case, our panelists are under a little more pressure, because they only have 10 minutes to do their presentations. We appreciate, though, very much their involvement.

Let us start with Ruth Brenner from the National Institute of Child Health and Human Development to update us, Ruth, on the National Children's Study. Thank you so much.

DR. BRENNER: Thank you. I'll try to go through this briefly and stick to the time frame.

I'll be providing first a background about the National Children's Study, an update on the current status, and the future timeline.

The National Children's Study was authorized in the Children's Health Act of 2000. In the Health Act, the language is here. It authorized NICHD to conduct a national longitudinal study of environmental influences,

including physical, chemical, biological, and psychosocial influences on children's health and development.

This slide outlines the study concepts that were largely derived from the Children's Health Act, that it be a longitudinal cohort study beginning prior to birth, and continuing through age 21 years, that this study be national in scope, again, that it be a study of environmental influences on children's health and development with environment broadly defined, and that the study be designed to allow measurement of both chronic and intermittent exposures.

A number of additional study concepts have been defined from both the Children's Health Act, subsequent workshops, and work of the Federal Advisory Committee and the Interagency Coordinating Committee. These are outlined on this slide, that the study by hypothesis-driven with primary outcomes related to child health and development, that there be sufficient power to study the common range of environmental exposures, but less common outcomes.

That we look at both the effects of environment and gene environment interactions on child health outcomes, and that the study involve a consortium of multiple agencies, both in the planning and carrying out of the study. Finally, that the data collected serve as a national resource for future studies.

Focusing now on the rationale for the National Children's Study, why the focus on children? Well, first, children have increased vulnerability to a number of environmental exposures. There are also critical windows of vulnerability, particularly early in development in utero when many of the organ systems are forming.

Children have immature mechanisms for detoxification and protection. There are also differences in metabolism and behavior that may yield higher effective exposures when children and adults are exposed to the same environments.

This is a slide taken from Selevan and published by Selevan in Environmental Health Perspectives that looks at some of these factors. I won't go through all of them in the interest of time, but if you just look at the top row, you can see that looking at surface area to body mass ratio, that ratio is higher in infants than in children, and higher in children than in adults. There are a number of other domains that you could look at and see how children actually have higher exposures to environments when placed in the same environment.

So why now? Why do this study now? First, there has been increasing concern about numerous exposures with suggestions that these exposures lead to adverse outcomes. The types of exposures range from changing

social environments, to increased exposure to the media, to exposures to new chemicals that have been introduced in the environment.

Additionally, there is an increase in concern about diseases and conditions of children, some of which appear to be increasing, such as obesity and possible autism, and attention deficit and hyperactivity disorder. At the same time, there has been growing experience with the effects of exposures and how they affect child health outcomes, particularly exposures in pregnancy and early childhood, like lead and fetal alcohol. There have been advances in technological capabilities, many of which you've already heard about today.

Finally, why a longitudinal study? Again, most of this has already been discussed today. It allows inference regarding causality, it allows a study of multiple outcomes, and simultaneous and sometimes synergistic effects multiple exposures.

It allows study of mediating pathways between exposure and disease, recall bias decrease, particularly in relation to exposure. Particularly important for children, it facilitates the study of development trajectories and how environmental influences at a particular point in time can affect these trajectories.

This is just a schematic of the multiple levels

of measurement that we anticipate in the Children's Study. There will be community level measures of neighborhoods, schools, and communities, measures of the social environment, friends, family, and organizations, a number of individual factors, and how all of these interact with genetics to affect health and development over the 21-year time period.

Now turning to the recent milestones and the current status of the project. After a number of meetings, including deliberations of an expert panel and recommendations from the Federal Advisory Committee in June of 2004, the decision to utilize the National Probability Sample was announced. Shortly after that, the study plan was developed, and this was first presented in September of 2004 to the Federal Consortium. Later in November of 2004, the study plan was made public as part of the request for proposals for the Vanguard Centers.

At the same time, a request for proposal for the Coordinating Center was released, and we published the "Growing Up Healthy" document, which I think was included in the packet. If it wasn't, I brought extra copies with me.

Briefly, the National Probability Sample, the first stage was drawn by the National Center for Health Statistics, 101 study locations, which are, for the most

part, single counties, although in some rural areas, it involves multiple contiguous counties. We draw from the full list of all counties in the United States. Thirteen of these locations are self-representing locations. Those are locations with higher populations. We anticipate a large number of births per year. Sixty-two are metropolitan and 26 were non-metropolitan locations, primarily rural locations.

In the second stage of sampling, we will be selecting segments or groups of households from within the study locations. We anticipate a highly clustered sample to facilitate study of community characteristics, as well as to increase the logistical efficiency of the study. Therefore, we anticipate a few number of segments within each location.

We will be soliciting input from the successful offerors to help define the segments. There are advantages and disadvantages to using traditional ways of defining segments which rely on Census boundaries versus less traditional ways like school areas. We will be asking offerors to help us in defining the segments and seeing what is possible within their locations. But to maintain the integrity of the sample, the offerors will not do the actual selection of the segments. That will be done by the data center in collaboration with the statisticians from

the National Center for Health Statistics.

This is the study map. These are the 101 locations that were selected across the country.

The next step was the selection of the vanguard locations. From the initial list of study locations, eight locations were selected to potentially serve as the vanguard locations. The vanguard locations will start data collection a year before the other locations, and will serve to pilot our procedures and modify them before we have the full complement of study locations on board.

Two certainty and four metropolitan, but non-certainty and two non-metropolitan locations were randomly selected. This included two locations in each of the four U.S. Census regions, and this map shows the eight locations that were chosen to potentially be vanguard locations.

That's an important distinction. Offerors were asked about potentially versus actual vanguard locations. Offerors were asked to propose procedures for data collection in one of those eight areas.

However, the number of awards that is made is dependent upon availability of funds and the quality of the proposals that we receive. We anticipate a total of three to eight awards. Therefore, somewhere between three to eight vanguard locations.

There will be no more than one award for

collection of data in a single location so we won't have two entities collecting data in the same county. If there are three awards, our goal is to make one award in each of the three categories of certainty, non-certainty, and non-metropolitan.

In addition, if there are four awards, our goal is to have one vanguard location in each of the four Census regions. The reason for this is so that we can get as broad of an experience as possible in the vanguard phase so that the experience can be applied to development of the procedures for the full study.

A few other aspects of the study plan. Again, we'll be enrolling women and, when possible, their partners, prior to or early in pregnancy, with follow-up of children until 21 years of age.

For the main locations, the enrollments over a 4-year-period in the vanguard phase, there is an extra year, so it is five years. Data will be collected in both face-to-face visits and remote data collections, and will include questionnaires, interviews, environmental samples, and observations both in the home and in the community. Clinical and behavioral assessments, again, both in the home and in the clinical setting, and a number of biological samples.

This is the proposed schedule as it appeared in

the study plan. There is a total of 15 face-to-face visits proposed, with additional visits for those who are enrolled preconception. You can see they are spread between home visits and clinic visits, and then one visit in the hospital at the time of delivery.

In addition to the challenges that were outlined in the previous slide, these are some of the challenges that we face in the data collection aspect. Certainly the combination of a probability sample with actual data collection conducted through the Centers of Excellence is a new design, and something that we're hopeful will be successful.

I think I mentioned the end date for receipt of proposals was a couple of weeks ago. It looks like this has fostered some interesting collaborations. We're hopeful that this will be a successful strategy.

We also propose to collect multiple levels of data in a variety of settings. I have just given an example of some of them, environmental specimens in the home, biologic samples at the time of delivery which are going to require relationships with multiple hospitals since we're using a community-based approach, versus the hospital recruitment, and a number of measures in the community.

We also want to capture both intermittent and

chronic exposures, and we hope to capture those exposures during critical periods of development. It's the combination of these two challenges that led to the preconception component of the study, to get those very early intermittent exposures, those early exposures in pregnancy that are sometimes short lived.

The projected timeline. Again, the closing date for receipt of proposals for the Vanguard Centers and Coordinating Center were last month. We hope to select the initial centers, the Vanguard Centers, in late 2005, and to complete and pilot the initial protocol in 2006.

We hope to enroll the first participants in the initial centers in early 2007, and to select additional centers in 2006 and 2007. The first preliminary result should be available in 2009 to 2010, and we'll continue to analyze data throughout the course of the study.

Finally, we've had ongoing and will continue to have ongoing meetings, peer reviews, workshops, and consultations. I just wanted to mention one of those. In September of 2004, we had a workshop on the collection and use of genetic information. This brought together experts in the federal government to explore opportunities and challenges, and provide recommendations to the National Children's study.

The focus was on appropriate collection and

storage of biologic samples. There is a workshop report that will be available at our website, probably at the end of this week. This is the website, if you want additional information. Again, I did bring, if anybody is interested, I brought some additional copies of the "Growing Up Healthy" document.

DR. TUCKSON: Thank you very much, Dr. Brenner. We very much appreciate that.

Now, let me invite Stephan Fihn from the Department of Veterans Affairs. Stephan will be followed by Alan Guttmacher, and then by the committee's own Muin Khoury.

DR. FIHN: Hi. I'm Steve Fihn. I'm going to try and make this very brief, because I know you are running behind schedule. Some of the material I have overlaps with what has been presented. I have to say that our planning is in the very early rudimentary stages. Really we don't have a formal plan. It is a great honor and privilege to come and talk to you all, just to sort of give you an idea of what we've been thinking about.

Basically this has been an idea that has been evolving with the Department of Veterans Affairs now for about two or three years. Many of you may not know that this is the largest integrated health system certainly in the United States, and potentially elsewhere.

We do have an integrated intramural research program. So to many people, it is thought to be sort of a natural thinking to whether or not the notion of both research in genomics, as well as clinical genomic medicine, could be brought to bear in a system like ours.

The goals of this program really would be three-fold. Much of what has been discussed is research and development related to genetics. This would be particularly in regard to clinical programs that would target drug response and prevent adverse reactions.

We already know now that there are commercially available tests that relate to genetic susceptibility. There is no doubt that there will be many more coming onto the market in the scientific marketplace in the very near future.

One of the questions we have is how do you implement these sorts of things in an actual clinical health system, and can we early in this process develop the research and development for these kinds of tests and intervention within a clinical health system? Obviously we'd like to pursue the same kinds of research that have been described here in terms of understanding better roles of genetic factors in both the prevention and causation of disease.

Then we need, like everyone else, to think

about what the information systems look like for collecting and making these data available.

The obvious question is why would the Department of Veterans Affairs be doing this. I think that's a reasonable question. As I said, it is a large, integrated health system with a very relatively stable patient population.

The turnover within our system is far, far less now than in commercial care these days. It is a very large system with somewhere around 5 million active users. We probably have the most advanced electronic health record in the world which collects copious amounts of data, clinical, administrative, and demographic.

As I mentioned, we have a very large intramural research program. Many investigators are already doing genomics at a very small scale. One of the goals of course would be to coordinate and pull much of what is being done together into a more organized and centralized activity.

Again, as a health care system, we can't ignore this sort of incipient issue, the clinical issues that are I think on the horizon. The other thing is we have actually now had an opportunity to discuss with veteran service organizations and with patients, and somewhat surprisingly, we often hear about patient concerns.

There is also a great desire among patients in

our system that we've heard obviously done with all of the necessary ethical and administrative controls and governance. But given that, they think this would be an important part of the medical care they receive, and actually have given a lot of support and enthusiasm for thinking further about this effort.

There are a lot of existing resources, as I mentioned already. We have already got several sanctioned DNA repositories. Many of these have emanated from ongoing clinical trials or other research. I suspect, like many research organizations, there are probably other smaller biorepositories in our system that really aren't registered, and that we don't know about. That's one of the issues, to try and get a handle on all that is already out there.

We are very, very early in the planning. Of course, it has been very interesting to read and hear about what other people are thinking technically and technologically. We have a lot to learn and gather, I think. Possibly by being a little bit behind the curve here, we can, as was mentioned, benefit from the work of others, and do things in a way that will be congruent with other studies that are ongoing.

We are looking at a number of collection techniques, as well as obviously we are not going to go

out, as was suggested in the biobank, and immediately enroll 5 million people into a database. We discussed all sorts of phased entries and variable specimen collections, and probably, like the other studies, will settle upon a hybrid approach which involves a combination of those.

One of the issues, again, as we're in a slightly different position because we're not exclusively a research organization, we're not a private foundation or corporation, we are a federal health care system, we would obviously insist on absolute control and ownership over all of the materials and information that were gathered as part of this effort.

We already have in place because we are a research organization, a fairly stringent set of policies for human subjects, protections, intellectual property, conflict of interest, privacy, and scientific merit evaluation.

We are also in the process of designing additional further protections for this in particular, which would, again, like the other projects, involve an independent, separate oversight board composed of both federal and private representatives.

Issues that we've struggled with are no different than what it sounds like that everyone else has struggled with. Governance and protection of

confidentiality. A particular issue, such as some of the other studies, is one of our strengths we think would be to link any data that we collected with our electronic health record.

Of course, this presents lots of questions as far as confidentiality and privacy. They are not completely new to us. Our health record obviously already has a lot of extremely sensitive information in it about a patient's HIV status, drug and alcohol, and so we really feel like although we need to be absolutely certain, this isn't completely new ground for us.

We are particularly sensitive to the notion of exploitation of patients. As I said, we've got a very loyal group of patients. Enrollment in our studies, the agreement to enroll is often in the neighborhood of 80 to 90 percent of patients who volunteer for studies, and retention rates are often in the mid to high 90 percent.

So I think because of that, we feel a very special reason to make sure, because veterans tend to feel a special bond to the Department of Veterans Affairs, that we have to be absolutely sure that there is no sense of taking advantage of patients, either with their participation in the study, or the use of information that is gathered.

We are working hard on collaborations. We are

talking to several other federal agencies, particularly in this period of budget austerity. We think it is really important for us to think about what we can do collaboratively as opposed to independently. We are, as I said, looking very carefully at the logistics, who the patient sample would be, and how it would be enrolled.

Our thoughts are that we will actually do this through our clinical programs. I mean, essentially we've got labs, 800 labs already around the country that could assist in specimen collection. Of course, we have to deal with transport, storage, and all the rest. It has been discussed.

We need to think about what additional unique exposure data we would have to collect from patients, and how that would happen. Cost is a big issue. We have not figured out precisely how this would be funded. Our current research budget in and of itself is insufficient to fund this effort. My suspicion is it would be through special programs through the Department of Veterans Affairs, as well as collaborations with other agencies.

A big issue that has come up early in ours is the intellectual property issue. There are strong commercial interests in this kind of information. We have really had to grapple early on with that.

I'll just stop there, since I think the issues

are similar to other folks.

DR. TUCKSON: Stephan, thank you very much for your presentation.

Let me invite Alan Guttmacher from the National Human Genome Research Institute, who has been very active in trying to get something launched themselves.

DR. GUTTMACHER: It's a real pleasure to be here and talk with the committee about something that I think that many of you have expressed interest about. The committee has heard something over the last six to nine months about a group that was meeting at the NIH to look into the really scientific questions about a possible large U.S.-based gene/environment.

Actually, I'm going to quibble with my own title slide. Even though we call it study because AGES is an easy acronym to be able to refer to, this as a sort of working concept, it is really more of a resource than a study. I think for study, the word "study" to many people implies a kind of controlled thing that is really hypothesis-driven. You have a specific hypothesis, and you're going to do a study to answer that hypothesis. We think of this as more hypothesis informed rather than driven. That is, it should be a large resource available to, as you'll see in a moment, basically the entire research community to be able to answer a series of very

interesting hypotheses and questions.

You have to have some sort of exemplar or hypotheses as you design something like this, because you might want to say gee, if it couldn't handle the following kind of question, why bother having this resource? But on the other hand, if we're thinking about large, longitudinal studies, one of the things we kept in our minds as we thought about this was they obviously will be providing data for years to come.

If, for instance, using the model, as many do when they think about these sorts of studies at Framingham, if you had gone back to the original days of the Framingham study and asked them to define the hypotheses which they would be using the Framingham study to answer in the year 2005, we would have done a pretty poor job of that.

We think the same kind of thing for these large longitudinal studies. You have heard this from many of the speakers before. The one needs to really be thinking very far forward, and therefore really thinking beyond our ability to think and to be aware of that as we go into it.

So obviously there are various kinds of approaches to discovering and quantitating the genetic and environmental contributions of disease risk. We have been talking about those all morning. Case-control studies and prospective population-based cohort studies. Case-

controlled studies are great, and that's perhaps the most important part of this slide, that even those of us thinking about this are clearly cognizant of the idea that case-controlled studies are wonderful things, and that we need to continue to have those for biomedical research. But there are some things they can't do.

Teri Manolio and others talked about some of the things that they could do and could not do. Amongst the aspects that Teri talked about, or particularly emphasized, are the bias towards the more severe end of the disease spectrum. This recall bias which Teri spoke about was in terms of both environmental exposures and family history.

For instance, there are several here who have done some teratology research over the years. We certainly all have learned the lesson that cases tend to have different memories from controls. Very importantly, the inability, using case-control studies, the limited ability to identify predictive biomarkers that signal the future onset of disease and to have good information about those controls before they become cases, because of course we want to have those early biomarkers.

Now, as you well know, we've heard about many of the other countries that are planning large population-based studies of genes, environments, and

health. Why doesn't that suffice? Those are going to be wonderful studies. But there are some problems for those of us in the U.S. in terms of utilizing these.

These include, and there are others besides these three, but perhaps the three major ones that other countries do not reflect are the population groups, no matter how one defines population groups. But the population groups in the U.S., particularly those very groups that seem to be at present most involved with having health disparities.

Other countries do not reflect the environmental factors found in the U.S. This will vary from country to country in how well that reflection is found, but it is not a full reflection of some of the environmental factors in the U.S. Be they the physical environment, social environment, or other kinds of environment.

Also this question about access of particularly U.S. researchers, but researchers in general, to data from other country studies will, as you've heard, be limited. So for all of those reasons, we thought there was reason to think about a U.S.-based study. Many of you will know about this, it is available in the materials. I think it is in everyone's binder that Frances wrote an article last summer, the case for U.S. prospective Cohort Study in Genes

and Environment, which I would refer you to it. It outlines many of the reasons for thinking about this.

A working group was convened, and these are the members of the core working group. I should also add that Teri Manolio's name does not appear in this. That's because she, along with Frances and I, were surfing the NIH perspective helping to sort of pull this together and organize it. Teri was a very active participant. She mentioned before being honest about her relationship with the Iceland group. I'm not sure why she refused to mention her relationship with our group. Perhaps she was a little worried about what I might say.

(Laughter.)

DR. GUTTMACHER: It shows how well she knows our group. Besides these folks, there were a number of subgroups, which you'll see here, which included another 50 people. So there were a total of about 60 folks from both the United States and from outside the United States involved in helping us think this out over the last, as I said, six to nine months.

So what are the major recommendations? I would emphasize major. The more detailed kind of information, I'll tell you at the end of the talk how to find that. But let me just sort of skate through some of the major ones since time is limited.

At the end of the day, the feeling was that cohorts should be chosen to match the most recent U.S. Census on six different characteristics. In terms of age, in terms of sex, in terms of race/ethnicity, in terms of geographic region, in terms of education, and in terms of urban versus rural residence.

It was also felt that the household should be the primary sampling unit, and that roughly 30 percent of cases should consist of biologically related individuals. I would like to point out that's not a floor, it's a target. In fact, there is an advantage to holding it not much above that, as well as an advantage to getting somewhere towards that.

It was also felt that the cohort should be a significant size to achieve adequate power for most common diseases and quantitative traits. If that does not seem obvious to you by now, you haven't paid very much attention this morning.

What does significant mean? Well, we did a number of various kinds of models to look at it. This is one that looks at the minimal detectable odds ratio contributed by a genetic variant after five years of follow-up, looking at various diseases in terms of their incidence per 100,000 in the population per year, with the assumptions up there of 80 percent power, and looked at

various cohort sizes, 200,000, 500,000, and 1,000,000. To no one's great surprise, the larger the cohort, the more data you get.

We also looked at of course because we weren't just interested in this alone, but also looked at minimum detectable environmental odds ratio after five years of follow-up for the same spectrum of disorders in terms of incidence.

Finally, we looked at it in terms of gene by environment interaction, which of course is perhaps what we'd be most interested in after a five-year follow-up. Now, there are a number of assumptions. Part of what this really presents is that there is no sudden sweet spot or something. There is no number where you suddenly say gee, this is a number you should get. Obviously the smaller the study, the easier to do. So if there is some magic number beyond which you don't get much added information if you get larger, no, so any kind of type of design of this is going to weigh the scientific possibilities versus some of the budgetary constraints.

What else did the group think about? Well, clinical exam obviously would be important. We thought that a baseline assessment should be done, which should be limited to four hours for various logistic reasons, that a core group of variables should be collected on all

participants, and other variables that would be age-specific to the participants.

Again, remember, the age of this resource would reflect the ages that we see in the U.S. population, that biological specimens should be collected, laboratory measurements done upon them, the specimens should be stored, the genotype and DNA sequencing would be done.

In terms of follow-up, that there would be telephone or email contact every six months, and that reexamination should be carried out every four-year periodicity.

Public consultation. We should also add that in here. Not just extensive, but early and extensive. There was a feeling that for something like this to work, for lots of reasons, there has to be, as many people alluded to before, that participants are truly participants, that they feel and deserve to feel a sense of ownership of this, that this would include various kinds of town meetings and focus groups before one even got started.

There should be an open-ended, informed consent with an encrypted database to protect privacy and confidentiality to the degree that one can protect it, but obviously being completely honest with participants about the limits of any protections. A central IRB would be highly advantageous, which is obviously something that many

would aspire to. It would not be unchallenging to pull off.

Data should be immediately accessible to all investigators who have IRB approval. I would like to underline this. This is perhaps a distinctive feature of this design. It is not unique, but certainly a very important part of this to us. That would not be something where a closed group of investigators would have access to the information, that much of what we were thinking about sort of came from a Human Genome Project-type model, and part of the power of the Human Genome Project was having data immediately accessible to as many investigators as possible.

Here one needs obviously to weigh that against various kinds of concerns for privacy and confidentiality of participants. We think by using IRB for approval, that one could pull that off.

So why do this now? Well, the urgency of discovery and validating these kinds of things, the same things that John and others have spoken about before. The opportunities to understand and address causes of health disparities, and also that we think this will be a powerful stimulus for technology development, as many of these kinds of population studies could be, we would like to use this to help do some of the work that Gil mentioned before about

really driving innovation in terms of measurement of both environmental factors, as well as better describing phenotype with new technologies.

Also, the potential to reduce skyrocketing health care costs by understanding better the etiology of disease and people's response to treatment for disease.

Finally, I will mention to you that by the close of business today, I believe there will be a full report of that working group. We've been working hard to try to pull it together for this meeting. We believe by the end of the working day today, and since we are federal folks, the close of business means midnight. Sometime today. If you go to genome.gov, that is the website. if you go to genome.gov/13014436, you will see a full report of the working group.

DR. TUCKSON: Thank you, Alan. What we can probably do, and maybe with the support of our staff, we can just get a little handout of that so that people will have that available. Thank you very much.

Muin Khoury, if you would give us the perspective from the Centers for Disease Control and Prevention. Then we will move expeditiously to the panel discussion that will be led by Hunt.

DR. KHOURY: Good morning. I guess I'm Speaker Number 10 this morning. By this time, you're all hungry

and tired, and you've heard it all. So I'll try to be very quick so that we can have some discussion.

I'll try to offer you a bit of a global perspective on how we can go about collaborating, whether it is case-controlled cohort studies, or what have you. A lot of what I have to say is in this letter of correspondence to Nature Genetics last year. But because of the format, I had to condense it to about 600 words. But a full report of this is available on our website.

Now, I have three messages to you this morning. They will reflect partly my own philosophy in what CDC is doing with global collaboration with many of the people you've heard from before, and I mentioned specifically a couple of things.

The three messages this morning is that global collaboration in Biobank and population-based cohort studies is needed. We are beginning to see the elements of that with P3G, U.K. Biobank, and others. I firmly believe one cohort study in one country is not enough, no matter how big that study is, whether it has 1 million people or 2 million people.

You have seen some calculations from Alan Guttmacher earlier. They were based on measuring one gene and one exposure or gene/environment interaction. You could see those minimal detectable odds ratios creeping up

as you begin to look at interactions. But if you are beginning to look at five or ten genes interacting with five or ten exposures, it is going to be quite challenging.

The second message I want to say this morning is that we need the process that integrates all of the human genome epidemiologic information, whether it comes from cohort studies, case-controlled studies, or other forms of studies. For the most part, most such data still come from case-control studies, and will for the foreseeable future. So we need to integrate that data as well.

Then the third, which I won't talk about today, is the need to link epidemiology with the evidence-based processes that use epidemiologic information for policy and practice. So there is a method to this madness. There is an epidemiologic approach that many of us have learned that applies not only to exposure, but genes. Because it is a huge problem literally, I decided to call it human genome epidemiology. Not because I have delusions of hugeness or anything, but because the problem is really huge on a practical scale.

What we deal with primarily these days is the processes of gene discovery, like the first speaker this morning who warned us that we need to kind of put on a different hat when we're talking about multifactorial

diseases. We are not really discovering genes for diseases X, Y, and Z, but looking at how genetic variation, whether it is 10 million SNPs or just three SNPs or whatever, affect the risk of diseases.

Why do we need epidemiology? We need epidemiology to characterize what we have in the population, the prevalence of the gene variance, how they affect the burden of disease in terms of relative risks, absolute risks, and also the burden of disease. Then also characterize gene/gene and gene/environment interaction.

You have heard about all of these by now, and you are sick and tired of the different study designs. They all have their advantages and limitations. But there are also hybrid study designs. You can conduct a cohort study for which you can measure exposures retrospectively.

For example, if you had collected information from a newborn blood spot and have stored it for many years, you can go back to that blood spot and measure both genes and environment. So you can still do a case-controlled study having the antecedence of exposures measured before the case and controls were collected.

There are a couple of myths and stigmas about association studies that are in the literature. The term "association study" almost is like a dirty word in genetics. I think it is a function of the poor quality of

association studies. Not because the field or the epidemiologic approach to association studies is bad. It is because the studies that are being done are really bad studies where the cases and controls come from different populations, and they are not even comparable, where you have both selection bias and all sorts of things.

Incidentally, both cohort studies and case-controlled studies are association studies. So there is that stigma that associates with that.

One thing I wanted to say here. Because of the lack of randomization, people talk about observation study as a second place class science. We don't determine who gets what allele. We are essentially randomized at miosis, or at birth. There is a movement, especially in Europe and the U.K., called the Mendelian randomization movement where it really takes the term "association study" and puts a randomized controlled clinical trial on it.

So basically it is randomizing people into Allele A and Allele B, and then look at the outcomes later. You don't choose which allele you get. It is just like you don't choose which drug you get from a controlled clinical trial. So we are taking the realm of association and making it closer to experimental design. We don't have time to talk about this.

Now, there is also this belief that cohort

studies are inherently superior to case-controlled studies. Or case-controlled studies are inherently inferior to cohort studies. I am here to tell you that a well designed population-based case-controlled study is far more superior than a poorly designed cohort study. Effectively, there are many things that can only be done in case-controlled studies, especially for rare outcomes.

Now, what we've done at CDC with a lot of global partners is begin to put our finger on the pulse of the so-called world of human genome academiology. We have this database of all the literature. This is only the published literature that we've been gathering since October of 2001. Essentially there are more than 15,000 association studies that are being published from only over the last three years. Those numbers are increasing.

Most of the data come from association studies. Most of them are case-controlled studies. There is an increasing number of studies that focus on gene/gene and gene/environment interaction, and there are a few studies that are just pure prevalence of different genetic variants in populations. But this is where the action is.

We are actually doing a 5 percent random sample of this database to look at the quality of these association studies. But other people have looked at that and have found that many association studies have poor

quality in terms of epidemiologic parameters.

NHANES was alluded to earlier. This is a study to look at the prevalence of the top 50 genes of public health significance that we are collaborating with NIH on to measure in the NHANES III, which is about 8,000 representative samples in the U.S. Those sort of 87 SNPs and 57 genes, and then trying to correlate those with the 2,000 phenotypic variables that already exist in the NHANES III bank.

This is another example of a population-based case-controlled study that essentially uses surveillance systems which are population based. These are surveillance systems for birth defects that are doing case-controlled studies for looking at genes and environments in relation to birth defects. There are about 10,000 cases and controls, and those numbers are going up.

If you have a population under surveillance like you have, it is equivalent to a cohort study of more than 1 million persons, or 1 million births, at least. There are other situations where you can do either massive case-controlled studies, or cohort studies like in managed care organizations.

So why do we need to integrate data? We have unmanageable amounts of data, two genes, three genes, four genes. For most chronic diseases, common diseases, we are

at least dealing with 10 to 15 genes to explain most of the etiology.

We have small sample sizes, whether we look at cohort or case-controlled studies. I'll show you a slide on that. We have small expected effect size of gene disease associations. Why? Because most genes are not expected to contribute by themselves to the etiology of most of these diseases. So the rule, rather than the exception, is to expect relative risks or odds ratios that are close to 1.3 or 1.4. So you need large sample sizes to discover them.

You need replication across studies. There is a lot that we have been dealing with with publication bias. There is heterogeneity that we have across populations and within populations, and you need to both generate and test hypotheses.

This is data from John Ioannidis from Greece, who is part of the HuGE movement, and has been really keeping his finger on the pulse of the published association studies. Most of these are small sample size, probably 200 or less. Most of the hundreds of gene disease associations have odds ratios between 1.0 and 1.4. This is sort of the peak at 1.2.

So how do we build the knowledge base on genes and population health? The answer here is all of the

above. But let me go through this thing with you. Single large population cohort study, a systematic synthesis of data from existing and planned cohort studies, a systematic synthesis of all data from either cohort studies, case-control, or all of them. The approach we're doing is number four, which is an accelerated systematic synthesis of both group and individual data using collaborative networks and consortia of all types of studies.

Of course, the right answer is number five here. But what do I mean by that? In 1998, CDC and many partners developed the Human Genome Epidemiology Network, which is truly a global, open-ended collaboration of both individuals and organizations that are interested in assessing the population impact of genomics on health, and how we can use genetic information to improve health and prevent disease.

The network has about 700 people right now from 40 different countries. It is wide open to anyone who wants to join it. There is a website with information exchange. There has been a lot of training and technical assistance through the form of workshops that we've been doing. Roughly on average, one a year.

We are developing the knowledge base, putting stuff together in terms of synthesis with quantitative methods of matter analysis, and we want to disseminate

information for policy and practice.

You have already seen the huge studies database that I alluded to earlier. In addition to that, we have been sponsoring in collaboration with six journals, systematic reviews of gene disease associations that many authors have subscribed to. We also have a database of 200 meta-analyses of different gene disease associations that is published elsewhere.

I mentioned the methodology workshops. I'll mention briefly the international biobank cohort study meeting we just had. We are in the process of forming a network of 14 different networks that exist in the world. Many of them are in cancer. Some of them are in heart disease. These are networks of investigators that have come together to pool their data and share information.

We are developing the sort of sharing of information between networks. Just by the way of going through this whole cycle from funding to publication, very quickly going through where things are right now. We are talking about different study designs, whether it is biobanks in one study, case-controlled studies or consortia, people do these studies, and then they report them. Then somebody else will appraise that literature, review it in the form of meta-analysis, cover methodologic problems and research, and then the funding cycle

continues.

What HuGE Net is trying to do is influence the circle here. We are collaborating with the various biobanks. We have focused primarily on this region here, but this will influence the study designs as well. I don't have time to go through this.

This is courtesy of Marta Gwen from our office that has superimposed this on an elephant, because depending on where you are in the world and what kind of studies you do, you only see part of the elephant. What HuGE Net is trying to do is to look at the whole elephant together.

This is briefly the meeting we just had in Atlanta in collaboration with P3G and NIH, courtesy of Teri Manolio. We brought together a small group that talks about the harmonization of epidemiologic data. This is the outcome of this meeting.

One of the outcomes was, and we are working on it, a statement that would be essentially important for publishing studies that are derived from biobanks. You might say well, the data won't be coming until 50 years from now. But if you have a statement, it refers to a movement in the world called Standards for Observation Studies in Epidemiology. This is a worldwide movement. U.K., Canada, and the U.S. have been setting standards for

epidemiologic studies outside genetics. What we are trying to do is influence the conduct of biobank projects and biobank studies through developing similar criteria.

The biobanks themselves are going to put together sort of best practices for the design and conducts of biobanks, and then update their online knowledge base with a register of studies and tools, and then having further meetings.

So in conclusion, these are my three messages for today. One cohort study in one country is not enough. There is more than one way to get there. I think all the ways will get us there. What we need to do is work all together to really look at this challenging area ahead of us, which is how do we make sense of the Human Genome Project.

Thank you.

DR. TUCKSON: Thank you very much, Muin. I appreciate it.

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. DESCHENES: 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.)

DR. TUCKSON: Well, thank you. Let me try this on the committee. We are going to take our break. Sarah actually came up with a very good idea which I think makes sense.

We will get our lunch. Well, you'll do what you need to do, and then you'll get your lunch. It is 1:20. So if you can do all of this in a hurry, and let's try to sit down here at like 1:30, which is impossible, but we're going to try. If I say 1:30, it will be 1:33, but we'll do it.

Then we will continue this discussion for the committee on this topic, so you don't have to switch gears. You're right there, you've got it all in your head. So we'll do this discussion, and then we'll give the full time that it was supposed to have for the committee to discuss what we've learned, and what we think we want to do.

Then we will take the section that would have been that and take care of the reimbursement discussion. You have paper in front of you to look at, which you can do. Then we'll be right back on track. Everything will be wonderful, and we'll end right on time. It will be just terrific. You should see it.

See you all in 10 minutes.

(Recess.)

AFTERNOON SESSION (1:35 p.m.)

DR. TUCKSON: Let's say if we were to have a discussion of about 45 minutes. Let's say we went to 2:15, and that would give us from 2:15 to 2:45 to do the reimbursement deal, which I'm sure we can get done in a half an hour. Of course we could. So how about we go to 2:10? We'll take this discussion until 2:10.

DR. WILLARD: Thank you.

I'd like to focus this back on the question that I raised 40 minutes ago, which is to try to say are there issues that we don't yet feel we have sufficient information on and/or are there specific gaps that we want to continue to study so that as the business of the committee, we can then advise the Secretary?

The only issue that was raised was the one that Ed raised. I'm trying to catch his eye, or his ear, but I'm not being successful, of having national IRB, or at least a global IRB rather than institutional IRBs. I'm not sure that specific issue is limited to these kinds of large cohort studies. The same kinds of issues are raised all the time for multicenter studies of which there has been hundreds, if not thousands. I might just raise that issue and see if anyone else reacts to it, or whether in fact

this is not one.

Michael?

DR. CAROME: I thought it would be helpful to give the perspective of the Office for Human Research Protections on the use of central IRBs for multicenter trials.

First of all, it's important to note that the office's regulations, which were written for the Department more than 20 years ago, have a provision that allows for cooperative or joint review arrangements for multicenter trials. So the authors of those regulations contemplated just these types of circumstances.

I will tell you, though, that when I joined the office about eight years ago, there was a general thought process that thought that local IRB review and IRB geographically located at the institution doing the research was better.

Over the last seven to eight years, the thought processes of the office has evolved, and has come to realize that joint review arrangements of multicenter trials certainly are permissible under the regulations, as I noted, and probably are good in many circumstances, given that many IRBs are now overburdened with workload, and having 100 IRBs or more review the same study when one or a few IRBs could review the same study, relieving that burden

is important.

There are lots of models out there. The National Cancer Institute has an IRB for adult oncology trials, Phase III oncology trials. They have recently set up another central IRB for pediatric oncology trials. These IRBs review on behalf of many, many sites. Upwards of 100. Again, that's certainly permissible.

A couple of factors that need to be taken into consideration is A, the need for the IRB when it reviews on behalf of multiple institutions and is going to approve research on their behalf, it needs to understand the local context of where that research is going to be occurring, or it needs to have some joint arrangement with the local IRB that lets the local IRB address a few limited local issues, but otherwise accepts the review of the central IRB.

The other thing is making sure you find individuals with appropriate expertise to review the research who are not conflicted. That is members of the IRB who are not going to be involved in the design, conduct, and the analysis of the trial. That issue has arisen on occasion with the NCI central IRBs, and we've worked with them to address that.

DR. WILLARD: So is it your sense that nothing you heard this morning would raise different issues that would require a different solution than is already

available?

DR. CAROME: There is certainly no need for regulatory or policy changes within the Department. The biggest factor has been institutions accepting a central IRB. For a variety of complex reasons that are sort of cultural, sociologic, and legal liability concerns, even within the use of the central IRB, there are institutions and major medical centers who are not willing to accept an IRB review from another institution or another entity.

Again, even when we say it is permissible, it is allowable, we encourage it for such multicenter trials, they either think our lawyers don't want us doing it because it puts us at risk of some liability, we do better reviews, so we're going to review it, and other things like that.

DR. WILLARD: Ed, are you satisfied?

DR. McCABE: Well, I was going to say, the issue is culture. You already mentioned that. I think if we're going to do the kind of studies that need to be done in the genomic era, we have got to help the local IRBs overcome this culture and assure them that in fact it is getting a better, more informed review by drawing experts nationally than they could ever do locally.

But I can tell you, at UCLA, this would be a major cultural issue for them. They seem to have gotten

away from this by developing a cancer IRB. So a separate IRB for cancer seems a little more amenable to these multi-institutional clinical trials. But we might have to help the institutions deal with the cultural barriers. That would involve education. That would be something we could recommend to the Secretary, because it would be a major educational undertaking to deal with this at all the institutions nationally. Especially if you're getting out to community hospitals.

DR. WILLARD: Does anyone else want to weigh in on that discussion?

Suzanne?

DR. FEETHAM: My comment is not related as much to a gap, but just as a reminder. As I listened to the presentations earlier and identification of characteristics and using the Census data, it is just a reminder that another perspective when you're looking at gene environment is the classification of biomedically underserved areas.

Again, with our agency and the focus on the underserved, this would be another way that investigators could identify their populations. Not just urban rural, but by the classification of underserved populations.

DR. McCABE: A different point, and that is I think it was wonderful what we heard today. Like Debra, I'm excited by the possibility. I think we aren't going to

be able to use the information from the Human Genome Project without these kind of studies. So it is absolutely critical.

On the other hand, I personally don't feel that I would have at this time all the information I needed at hand to say to the Secretary, you should support this study, that study, or some new kind of study. So I'm not sure how we can move from where we are now with this wonderful introduction that we had to getting to that point, but I would feel that if we were to make a recommendation, we need to move beyond where we are now. Or at least I would feel personally that I needed more information.

DR. WILLARD: Kevin?

DR. FITZGERALD: On that note, a couple of things are of concern to me, and I imagine to other people, too.

Perhaps veiled in the global question I raised earlier was a question that was trying to get at what you wanted. That is, what kind of information do we think we might need in order to go forward from here?

The idea in looking at the AGES or whatever they are going to end up calling the project, when Alan presented, I thought it was very interesting. In one of his slides, he said public consultation should be

extensive. They mentioned town meetings and they mentioned focus groups. I know those are two ways that are kind of hot right now for engaging the public.

But we could even make it a more general sort of question and say, if indeed as Teri mentioned, you do the best that you can do, what is that? Who determines what is the best we can do? Do we have that data? Have they looked at those studies? Where is that information? Maybe they have. Maybe that's out there. We don't necessarily have it together yet.

Then could we, looking at that information, at least suggest a process that would have a beginning where again, as was mentioned, the public would have some input into design? So this isn't our excitement being sort of sold to the public so that they will buy in in a sort of way, but to say no, they have to be empowered in this entire process. Then have standards or mile posts along the way to say all the way along, this is going to be a potential for public interaction, review, and evaluation.

I imagine, as we all do, that this information is going to be there, and it is going to grow and expand, and it will be shared among different nations, different groups, and that sort of thing.

So that in the end, we can say that this is something that the public is definitely a part of all the

way along. Again, I think we're going to run into questions later on, like what happens when you do find something? Especially in the United States. What does that mean? Is it only going to be available to some? If there is a treatment, is it only for those who can afford it or have the proper coverage?

So all those kinds of things I think need to be in from the beginning. That would be the type of information I think we could gather, at least at the beginning.

DR. WILLARD: Ed?

DR. McCABE: There's a model, not for this specific question, but for this kind of question. How do you engage the public? How much information do you need? How involved can they be? That's designed through focus groups. That's with Kathy Hudson's Center on Reproductive Genetics. The Pew Center, it's a Johns Hopkins Center.

So I know they have been coming out to the west coast to do focus groups. From my discussions with Kathy, at least, they have done a bit of a scientific approach to how much information is enough.

DR. FITZGERALD: Just to build on that, that's right. That group is one. There are a bunch of different groups that are using that. Part of that comes from work by Dan Yanklovich that he put together. So as I said,

there is material out there, and studies have been done.

I know that Canadians had an extensive process whereby they had focus groups, task forces, and town meetings to look at some of their health care issues. I think we should at least start to gather that information and see how we might want to build a process out of that sort of thing.

DR. GUTTMACHER: Hunt?

DR. WILLARD: Cindy first.

MS. BERRY: I was wondering, in terms of what we can recommend, if it would be appropriate for us to suggest to the Secretary that when the administration devises public health plans or programs, and I'm thinking obesity was one that Secretary Thompson focused on, and I'm sure cardiovascular disease or women's health issues, whatever it is, when they launch public education, public awareness, and other types of programs, that the Secretary always infuse into those programs at the outset, the genetic component.

So if maybe part of that big effort, whatever it is, would involve some sort of commitment in terms of funding studies like what we were talking about, enhanced funding, more than what is currently being done, so that it recognizes the importance of genetics in all of these issues, keeps the issue out in the forefront for the

public, and helps to educate the public appropriately.

So in public education campaigns, when the Secretary goes out across the country and holds the town hall meetings and all these other things, genetics is always there, whether it is just talking about a study, encouraging people to participate in a study, whether it is announcing an infusion of funds, whatever it may be, that our recommendation would be that the Secretary always include, or look to include where appropriate, a genetic component to whatever your new public health activities are. Maybe we can give a few specific examples.

DR. WILLARD: A point of information. The Surgeon General belongs to whom in the government? In HHS? Does he report up through the Secretary?

PARTICIPANT: Yes.

DR. WILLARD: Okay. Alan, you had a question?

DR. GUTTMACHER: And the Surgeon General is actually quite aware of genetics and its role in medicine. He talks about it almost every single speech he gives these days. He is very much into carrying the public health message of genetics.

I just wanted to make the point. I can hear many people in the committee share, well, many of us around the table have an excitement about the importance and the value of these kinds of studies. Also I must admit some

excitement with just the intellectual aspects of how one would design such a study.

But I should warn the committee that our experience has been with this working group that it took literally thousands of person hours to get this report that will be up on the Web very soon, to get it that far. I think the committee needs to think about how much does it want to suggest specific study design issues to the Secretary, or how much might it want simply to call to the Secretary's attention the potential value and importance of such studies and what are the design features that need to be considered for such studies to be effective, useful, and what are the questions about participation and community consultation, involvement, et cetera, rather than going too far in designing it.

It is going to be, I think, a challenge for the committee. If you want to move in this direction at all, it would be to figure how far to go with somewhat limited staff time, how far you want to go down the designing path versus just saying these are the features that need to be taken into consideration, these are some ways to look at them kinds of things.

DR. WILLARD: Muin?

DR. KHOURY: Actually, I have a couple of comments for the committee, and also a comment on what

Cynthia just said.

It is very obvious at this juncture in time that in order to take the Human Genome Project to the next level, which is to translate it into health benefits for the public's health or the population, that we need to understand genes and health. That as an initiative, I think this committee is very well situated to suggest to the Secretary that you need to do something more than just sequencing the human genome, which as HHS has spearheaded with DOE and others, that we need an initiative that measures the effects of genes on the population or the populations.

That statement I think is a no-brainer, but I don't want to put words in your mouth. Now, to get down from there to the level of one study, two studies, or three studies, you guys can decide how much more specific you want to go from there. I mean, you want to enhance sort of the leadership of HHS and push it a little bit, and also this issue that Cynthia raised earlier about the integration of genomics into everything that smacks of or smells of public health.

You mentioned obesity. I just want to mention here that this is sort of the basic principle by which our little office at CDC has been operating, which is to try to integrate the messages of genomics into whatever it is. We

have a group that's working on obesity right now. We are going to be part of it.

We have a STEPS initiative that is department-wide that involves HRSA, NIH, and CDC, which is a chronic disease prevention. Of course, our Surgeon General is very interested in literacy and promoting family history. So there is always an angle by which we can find that trigger, or the point of integration of genomics.

So I think these are the two points that I wanted to make. One is the encouragement for HHS to sort of develop agency-wide, multiple agencies coming together to figure out what the genome means for health, and whether it requires one study or three studies.

I'm not suggesting I agree with that, and I don't think this committee should design one study after all of the hours and many months of work that has been put into the ideal design of that AGES study. But you can make sort of overarching statements about the importance of these kinds of studies and what HHS can do.

DR. WILLARD: Reed?

DR. TUCKSON: I think I'm sort of headed where Muin is. I think the first and critical question is do we as a committee know enough to believe that we should make a recommendation that this is an area that should proceed?

It seems to me then that for me, I'm just

trying to write the letter in my mind, the letter to the Secretary that says, Dear Secretary, we believe that we need a large population study for the following reasons to answer the following kinds of questions that would benefit the health of the people.

Part of that phraseology, Muin, is what you said in terms of that now that you have the genome stuff, now you have to apply that. But you need to apply it and understand it in ways that lead to some kinds of describable deliverables, that we think it will improve the health of the American people in the following ways for the following reasons.

We believe that to achieve that, certain things need to occur, like the coordination of resources across the Department to determine the best use of available funding and money, to determine the number of studies and how they ought to interrelate so that this is efficient and it makes sense.

I think that to me is a letter that I think we could start thinking about sending. But the challenge is how do you fill in now the details there?

DR. WILLARD: Ed?

DR. McCABE: The one thing I would change in the opening paragraph of your letter is that I wouldn't specify a study. I was convinced by what I heard this

morning that it is probably studies, the question is how many studies, how should they be prioritized, and how should they go.

The other thing that I heard this morning and I'd like to mention that might be in the letter if the committee agrees is that this might be another thing that's a public/private partnership. Especially given the budget where it is today, given the amount of intellectual property that could potentially flow from this. We are certainly already seeing that come out of deCODE Genetics in Iceland.

I really think that this is one where, and I understand the Bayh-Dole rule and all of that, but this is one where I sort of feel that maybe there ought to be an investment up front from the private sector.

DR. TUCKSON: I would just say, Ed, I agree with you. I'll take it as a friendly amendment to my proposal. Instead of saying "a study," I wonder whether we could say "a coordinated activity." Because one of the things obviously in the stage where I'm at with my question was the sense, and I appreciate that Muin, Alan, and everybody, that they all play together nice in the sandbox.

At the end of the day, you don't really get the feeling, quite frankly, even though you all are talking, you don't get the feeling, especially when you have

somebody that is authorizing language already, and somebody else doesn't. You've got three multiple activities hitting against the same budget activity.

So I'd just like to sort of see it being explicitly more coordinated, whether it's one, two, or three.

DR. WILLARD: Emily?

DR. WINN-DEEN: So I guess I would go even a couple of steps further and say review all the existing studies, analyze what the gaps are between what is already going on and what we feel should go on, and then direct additional funding towards funding studies or study whatever is appropriate to fill those gaps.

I think you have to have sort of a three-phase approach. The first of which is there is already good work going on, right? We don't need to replicate the good work that's going on. The second is where are the holes? The third is then either specifically endorse a study, or just more generally, which is where I would favor, at this point in time since I don't think we're ready to endorse a study by name at this point, to say that studies to address the gaps should be funded by the U.S. government, and where appropriate with public/private partnership, and just sort of stop at this point.

DR. WILLARD: But let me push you on that point

a little bit. When you say "review the studies," what more information would you want? In what depth? I mean, what does the committee need to do to review them in order to have identified those gaps beyond what we heard today?

DR. WINN-DEEN: I'm not sure we need more than what we heard today. But it needs to be pulled together in sort of a coherent single document at least. Here is the state-of-the-art today, rather than a bunch of PowerPoint slides, some of which we got, some of which we didn't get to keep.

So I would like to see something that goes up. Here is the state-of-the-art, here is the gap analysis, and here is the recommendation going forward. The first phase might be just a letter that says this is what we're going to do, one, two, three.

DR. WILLARD: You're answering the question of what the staff was going to do when they finish the reimbursement report, right?

DR. WINN-DEEN: Well, maybe. It's a suggestion. I'm not sure that our group is necessarily the right one to do that evaluation. There might be another more appropriate group within HHS to do that summary and gap analysis. On the other hand, this might be the right group. I'm not sure, because I don't know everything about everything that goes on in HHS.

DR. WILLARD: Muin?

DR. KHOURY: May I be bold enough to push the committee to use the word "initiative" from the Department, instead of a "study?" Because an HHS-wide initiative can sort of achieve the purpose of what you're trying to do here, which is take the Human Genome Project and put it into population hands. That is sort of the spirit of this.

Now, in deference to the NIH, I guess it will all behoove you to wait to see that document that the group has worked on tirelessly for the last few months and see for yourself the amount of work that has gone into it. I suspect it has a background section and everything. It is not only focused on just the age of study, but it has much more than that. I mean, I haven't seen it, but I suspect it has all of that in it.

So I think as a committee, you can review that, and then you can recommend to the Department an initiative that takes that plus other activities that goes on within the other agencies, within NIH, CDC, and develop an HHS-wide initiative that could morph into one study, two studies, or 15 studies. I'm not sure how it is going to evolve. That study would be on the table as one of the considerations for discussion.

DR. WILLARD: Any other points on that question?

DR. TUCKSON: I just wanted to ask if Kevin could come back, then. Kevin, if right now we have as an outline here sort of that we would be thinking of sending a letter to the Secretary about explaining why this was important, that we would applaud the good work going on, the gaps identification, the calling for some analysis that leads to an HHS-wide initiative to address whatever the gaps were, and then the idea of putting public money and perhaps something about private money.

We haven't gotten to your point earlier around what the American people want. Where does that fit into this?

DR. FITZGERALD: Well, I guess it depends on how you want to look at the wording that you're using. So if you're talking about what are the gaps, as was mentioned, we haven't seen yet what the genome website is going to have on there, what the report says. I haven't looked at that data yet.

But again, it would be another example of the way in which the public can be engaged and empowered in this process. That could be seen as one of the gaps that needs to be addressed further. How well can that be done? Is this something that is of such importance and magnitude that it is going to be a significant problem? Or have we pretty much found ways to address this in constructive

terms so we can go ahead and figure that we're going to be handling these issues as they go along, because it will be part of the process.

I would just see that as one of the gaps for sure that would need to be filled in.

DR. WILLARD: I might raise, and I'm not sure I believe in this, but I'll say it anyway just to get it out here for discussion. That is I have been very impressed in the U.K. by a process or a group, I think it is the Human Genetics Commission or something of that sort, which was representative of the public at large, which in fact examined a whole host of issues that led up to the formation of the Biobank.

They traveled around the island, met with various groups of people, and collected that information. It was a separate group. It wasn't led by the MRC or the equivalent of any of the bodies that we have represented here, because it was really the public doing its work and registering its own opinions.

So my question of the United States is not the United Kingdom, but the question is is there a need for that kind of an arrangement before we would anticipate an HHS-led study of half a million to a million Americans who are going to have their bodily fluids sampled and stored for all time, and eventually perhaps leading up to having

their genomes sequenced when we can do it for reasonable dollars.

I mean, we are in a country right now where the Bank of America can't even protect records from members of the United States Senate. I'm not sure the public at large is prepared to assume absent an opportunity to weigh in on the issue, just assume that folks will get this right, and that people's medical information and genome information, potentially very sensitive information about medical conditions that they may or may not be susceptible to, that that somehow will be okay and will sit in a computer somewhere.

So I think there may be a lot to be gained by allowing the public in a very broad and far reaching manner to weigh in on this issue. This is the right time to do it. We did a reference sequence which wasn't specific to anyone. But before we kick off a much more extensive study that might involve a million Americans of many different ethnic groups which will have to be represented in one way, shape, or form, to allow all the representatives of those groups in fact to weigh in in a clear and deliberative manner. I'll throw that out to the group.

DR. TUCKSON: Did you convince yourself, by the way, while you were talking?

(Laughter.)

DR. WILLARD: I was just getting up to steam.

DR. LEONARD: I agree. In listening to the talks, I remember hearing the word "trust." You have to have trust of the participants. My immediate thing that popped into my head is can we create trust in the U.S., either of scientists, the government, or with the current environment the way it is. I don't know that that's feasible.

Maybe by doing this type of project, it would at least be a step toward building trust, which at this point, I think we're going to fall flat on our face.

DR. GUTTMACHER: Where are the data to support that? I'm just curious. Because, I mean, there are certainly other large studies out there that are collecting genetic information in a thoughtful way that we have not had in the U.S. Not to say that it's not a challenge, but I'm not sure that we're entering quite so dire of a situation.

DR. FITZGERALD: Well, I mean, just to address that a little bit. I think there is some data out there, and it may not be as extensive or as deep as we would like it to be. There are some issues where this has been addressed in a kind of different vein.

One has been say genetically engineered crops. Part of the idea that was wrestled with there was

everybody is thinking, this is all great, it's wonderful, it's going to benefit the public. Well, does the public think it's going to benefit the public? Then you say, well, they don't. Well, then that's a matter of education. Once they know what we know, of course they'll agree with us.

Well, that may or may not be the case. That gets back to these other sort of town hall meetings, focus groups, and that kind of thing. The whole point of that process is to begin this dialogue. What I would argue too, is that this is not just for this particular issue.

I understand, and I think pretty much if we took a poll of the people around the table, we'd all be convinced of the usefulness and the benefit of this extending what has gone on in the Human Genome Project. But I think Debra is right. We have to, as part of this thing, also recommend that the government build trust. This is just another stepping stone, and there will be something after this, and there will be something after that.

We have to look to the future to say what kind of precedent do we want to set now so we don't have to come back and revisit each and every one of these issues again and reinvent the wheel.

DR. TUCKSON: We've got five minutes to resolve

this.

DR. WILLARD: I've got Robinsue first, and then Muin.

DR. FROHBOESE: Thanks. As the representative from the Office for Civil Rights and the office within the Department responsible for the HIPAA privacy rule, I just wanted to remind people of the rule, and the fact that we are working with the public in general to really raise the consciousness level of consumers and their rights to privacy of their health information.

But we also have been actively working both with CDC and NIH, and have issued guidance with both NIH and CDC on research, both from the public health perspective, and more general research issues. Research specifically as it relates to the privacy rule and protecting privacy interests.

DR. WILLARD: Muin?

DR. KHOURY: As a follow-up on your comment earlier, Hunt, about the British way of how they went about it with the Generics Commission. I wish John Newton was here to explain more.

But if there is such a group in the U.S., I maintain to you that this committee comes as close to that, I mean, the name Genetics Health and Society implies that. You are advising HHS.

If you want to undertake sort of the martialing of the post-genomics or the genomics era and how to translate the genome into health benefits to help society. I mean, your group, if you decide you want to undertake such a process to help the Department undertake such an initiative, would be the right thing. That's up to you.

DR. TUCKSON: We need specific recommendations as to how to proceed. You've got four minutes.

DR. WILLARD: I can't read your name, so I'll call on you.

DR. FOX: I'm Ellen Fox.

DR. WILLARD: You're not Willie May, even though you're past the sign.

DR. FOX: Reed, in your suggestion regarding the wording of the letter, you mentioned looking at gaps, and then looking at where there were gaps, assuming the government would fill them. Perhaps in association with public/private partnerships.

I think there needs to be a little more attention, and there hasn't been much discussion today, but somehow I think we need to address the issue of the appropriate role of the government relative to the private sector.

I wouldn't want there to be an assumption that the government should just fill all the gaps that exist in

this endeavor, particularly when there is an opportunity for private industry.

Also when we were talking about public/private partnerships, I think we need to be very careful about that. I think that in the U.K., my understanding is there were some concerns among the public about the commercialization aspects. That was a particularly sensitive issue.

In our own experience in VA, this was I think the single most controversial aspect which caused us to actually completely reverse our course and pull back from our original thinking on the issue, because of significant concerns raised about the relationship between public and private sectors.

So I for one would like to see some language in this letter that acknowledges that tension.

DR. WILLARD: I have Joe first, then Alan, then Kevin until we get cut off by the Chairman.

DR. TELFAIR: I'll pass on my comment. I'll wait. That's okay. I'll pass on my comment.

DR. GUTTMACHER: And I'll try to speak very quickly. I think, again, I agree with Muin's point that this group is as close as we have to the U.K. Commission.

It seems to me that it gets back to this question of how far you want to go down the road of

designing the study. What would make most sense to me would be simply strong wording the letter to the Secretary that it is just completely vital to the success of any such study that community participation be often, early, frequent, ongoing, and giving ideas of the kinds of ways that might be achieved, rather than going out and doing that first.

We know that it is necessary, so just make it very clear that that really needs to be done, it needs to be meaningful, and it needs to use the latest state-of-the-art kinds of things to do it, and maybe invent some new ones.

DR. TUCKSON: I think we've got a good sense of a charge to our committee. We have a good committee that put together one heck of a discussion today. Clearly they are focused and know what they're doing.

I think the overall committee has given pretty good specificity as to first of all, there is a consensus that I hear that's very strong that we do want to communicate with the Secretary about this. I see a very strong consensus that we think that this is an important area that needs to go forward.

I think that we have agreed at least to charge our subcommittee with the task of fleshing out the first draft of a letter that would say why we think this is

important in terms of the health of the people. Why it is important, as Muin's language was, that says that having done the human genome, putting it into play is for the benefit of the health of the people. This is an important thing to do. So I think that's important.

Secondly, we do want in this letter to praise the good work that is already going on. Third, we're calling for some type of a gaps identification. We are then calling for a coordinated effort which we are using the suggested word "initiative" as opposed to a study that would address the gaps.

We are clearly saying that one of those gaps is looking at what is important to the American people, and seeing what we need to say there. We are saying that we would be calling for public money, but also perhaps, and this is something for you to look at in a little more detail, private dollars.

We just heard a comment around maybe even putting in something that has to do with the appropriate relationship between the public and private sector on initiatives such as this.

Then finally, what we didn't resolve, but I think we have given a mandate for you to look at is this notion then of the question of establishing trust, which I think is related to the gaps around what American people

want, and how that might be phrased.

I don't think we were as prescriptive as the rest of the letter, but we leave it to you to take the sense of it.

Kevin, I'm not sure whether you're on that committee. You are on it?

DR. FITZGERALD: I'm not on it.

DR. TUCKSON: But I would urge you to connect to the committee and get your points in.

With that, I think we have the expectation, Hunt, that as the Chairman of that subcommittee, that we will get a report back from you with a draft before the next meeting. Our commendations for an excellent set of presentations today.

All right. We're going to move to something which, again, we need to be very disciplined on our discussion of this billing and reimbursement. You have a page in front of you.

Does everybody have it? I'm going to just take you through really quickly just the logic of this. Then when we discuss it, we need you to be focused in on the logic and on where you are on the page. We can't have people going all over the universe today on this. We've got to bring this to closure.

Number one. What this paper says is let's get

on the table or off the table. The question of whether or not today genetic counselors who are certified ought to be able to bill independently, because they in fact have a certification that would thereby make that possible.

So the language sort of says right now, do we believe that there is sufficient reason, is there a reason overcoming the barriers that we identified in this report, is there a reason to warrant, and are there sufficient evidence, criteria, and processes that would support a recommendation that non-physician health professionals who provide genetic counseling services that are deemed qualified should be able to bill directly for their services.

Would this apply to all payers? Or only public insurance? Such a recommendation then would in fact allow these health professionals to independently practice genetic counseling. That's first.

If we said that that were true, if we believe that that is a recommendation that we would want to make, then the question would be how you would implement something like that. Would you take as a strategy that licensure where available, then be able to use it because they had licensure in a certain state?

In those states where it was not available, that because you were recognized by the ABGC, or the GNCC,

that that would be sufficient to allow that to occur. Or that you'd leave out the licensure part altogether and just simply say, let's just make it the certification. Or that the Secretary would use his leadership to influence the establishment of a single body that would oversee the certification of providing these genetic counseling, similar to the role played by the ABMS for physicians that would have the functions as listed there.

This "or" after that should not be there. It should simply be that this needs to be done expeditiously if it were to occur. So again, it would be that the train would start to leave the station, and while it is leaving, the Secretary would be asked to use his influence to help facilitate the creation of this body that would continue to study it, even while the event was already begun.

If you believe that there is not sufficient evidence to do this today, that we're not going to make this recommendation and we can't make that recommendation, would we then say okay, we've got to urge the creation of a body to answer the questions that we are unsure about, and that that needs to be done expeditiously with perhaps some hope for time scale to determine the answers to things like which providers are qualified under what conditions, under what supervision, and how they should be reimbursed.

This analysis should also assess the

effectiveness and value of genetic counseling as delivered by various health providers in different settings, assess how barriers to billing and reimbursement are affecting patient access, and so forth. So those would be the things that would be called for urgently and quickly to get done.

Then in the interim, while those things are happening, whatever it is that is going on, because it will take time, either one, Option A or B, there are certain things that we worked hard on yesterday to agree on.

That was in the interim, the Secretary should direct government programs to reimburse prolonged service codes, HHS with input from the various providers of genetic counseling service should assess the adequacy of CPT and E&M codes, non-physician providers who are currently permitted to bill directly under any health plan should be eligible for an NPI, and then finally, that for those who are billing incident to a physician should be able to utilize the full range of CPT and E&M codes. So that's the logic, that's the flow of it.

So the first thing to get on or off the table is what do you believe about the need and/or, relatedly, the ability to make the determination right now that genetic counselors who are in some ways certified should be able to counsel independently and bill independently? What is your thought about that? Put it on the table, or take

it off the table? The floor is open.

And Debra Leonard is not here. Let me just get her point in right away. Debra has been emphatic to the point of she jabbed me in the chest when she was talking, make no mistake that she believes that the answer is yes, that they should be able to. I'll get to what her strategy for implementing that is. But she is one person that says it should be done now.

Barbara?

MS. HARRISON: And I as well say an emphatic yes. Under yes, I think that we should say the first statement wherein states licensure is available, skip the second one and go to the third one where the Secretary would use his leadership. Also --

DR. TUCKSON: That's all. You only get on that one.

MS. HARRISON: Just for clarification.

DR. TUCKSON: Okay.

MS. HARRISON: The "in" in the interim part is going to be there regardless? Is that what you were saying?

DR. TUCKSON: Yes.

MS. HARRISON: Okay.

DR. TUCKSON: Yes, that's already there. Okay.

DR. FRIES: I also fully agree that there is

sufficient reason to recommend that they be able to do this. I think that genetic counselors and certified nurses have established a training program and an evaluation process.

I think it is very clear. I think we also had adequate demonstration of that before. I think that if you look at the proof of practice, it is already demonstrated. So I emphatically believe that yes is the answer for this. I would recommend that the third comment there, "Secretary using his leadership and influence to establish a body of certification," I think that would move towards assisting this group in obtaining licensure.

Once they had licensure, this would be a no-brainer. It would already be established.

DR. TUCKSON: Okay. Other comments, please?

Yes, sir?

DR. ROLLINS: I think that licensure and certification is not sufficient to make a recommendation that non-physicians be able to bill directly for services.

From our discussion yesterday, as I said, if we're going to be using evidence-based medicine as a basis for making recommendations, they did not provide evidence that non-physicians were able to effectively make those type of determinations compared to other groups.

There were not enough studies from an

evidence-based perspective which would justify my opinion.

DR. TUCKSON: So we've got three that are saying yes, and one so far saying no.

MS. BERRY: I would say yes with the caveat that when we were talking about Medicare and I deferred to James and others, we can't, and the Secretary can't just declare, we are going to now allow these folks to directly bill Medicare. I believe it would require some sort of change in the statute.

Correct me if I'm wrong. If that's the case, then our recommendation should be more towards urging the Secretary to work with Congress on legislation that would do that. In doing so, it would be incumbent upon the different groups to convince the sponsors in Congress and to convince the Secretary to provide the evidence that James is talking about.

DR. TUCKSON: Okay. So James, you have to take away your philosophical hat. We are not at a technical question purely in terms of if we were to make such a recommendation, now we are talking about the language.

So can the Secretary cause this to occur, or does it have to be a Congressional change?

DR. ROLLINS: I think it would require a Congressional change. But also, I would say that if there were some type of demonstration through the use of some

types of studies which show that they were as effective --

DR. TUCKSON: Different issue.

DR. ROLLINS: Okay.

DR. TUCKSON: Okay. So the answer is that for those who are saying yes, that this should happen, the technical way in which a yes gets transmitted to the Secretary is that we recognize that he or she may not have the power to by the stroke of a pen, cause it to occur, but it has to work through the Congress. That would be the language. So that's just a technical issue.

MS. BERRY: Just for Medicare. Now, the private sector, that's a different thing.

DR. TUCKSON: Right.

MS. BERRY: We can make all sorts of recommendations that is harder for the Secretary to influence.

DR. TUCKSON: All right. So we're at four to one.

DR. FITZGERALD: I would also like to say yes. Maybe take into consideration the fact that when we talk about evidence-based medicine, we always have to look at who were the people who set the standards for what counts as evidence? How do we go about getting that evidence? What sorts of motivations have there been in the past to get that evidence?

If this profession is seen in its proper role as a profession to be reimbursed, then of course that will also help I think instigate more research into how it can be done better, which of course will be based on studies that will look at the evidence. I'm sure the evidence will confirm what we're saying, but it will also lead to the sorts of improvements and the sorts of gathering of data that we're talking about that would also be a good thing.

So in one sense, there is a bit of a Catch 22 here in the sense that there hasn't been the motivation, and there hasn't been the emphasis in the past to gather the evidence in such a way as to answer those specific questions. I think people's experience can also be seen as evidence.

DR. TUCKSON: We're at five. By the way, I did a disservice to the conversation by not making one statement up front. Let me rush to make it. It is this.

We had a lot of discussion yesterday about this issue that got to the nature of respect for these professionals. I have talked with almost everybody on this committee at some length about these issues. The one thing I want to take off the table for this discussion is that there is not a single person around this table who has anything but respect for the professionals who are working so hard to do this kind of counseling.

Those who may feel differently about this issue do not come at it because they don't care or respect their colleagues in this field. I want to just make sure that that is on the record.

I think it is a very important point, because otherwise, it could have the effect of chilling the discourse. If you are viewed as whether or not you are up or down on genetic counselors, you get beat up when you walk to McDonald's.

I don't want that to be on the table. That is not appropriate to do that to anybody on this committee. Let's move around and see if there is anybody else.

DR. TELFAIR: Thanks, Reed.

You saved me from having to say that. That was going to be my comment, because I'm voting no on this. I'm voting no because I do think that it will be a stronger case if you take the effort of building the evidence.

Clearly what is in place right now, from my understanding from yesterday, and if I heard it wrong, I apologize. It is still in the early stages. Everything is in the early stages. Even those who have received this level of verification are only two or three years out. So there really hasn't been enough time to build that evidence.

It seems to me that we need to really push

doing that a little bit more. So that's where I'm coming from. I am one of the ones that really pushed to expeditiously get it done. I think it can be.

DR. TUCKSON: Agnes, Hunt, and then we'll go around.

MS. MASNY: I would say yes, that we should go for the first proposal. The one thing I think that when the committee presented yesterday is that I don't think that they were asked to actually present all the evidence base about what we're discussing now that the genetic counselors or people that are providing these kinds of services actually do provide efficient, cost-effective, or whatever it was.

I think that maybe if in fact we wanted that, that we could ask that specifically for this committee. But I don't think that would be necessary. I think that maybe if it had to go to Congress, that that information could be presented from the group itself to go along with that recommendation to Congress.

I would though say that I would rather have that without reference to licensure, because I think licensure is affected mostly by states. I don't, again, from the Secretary's perspective, know whether he has jurisdiction over state effects, certification by AGCC, GNCC, and other certifying organizations, since there are

other certifying organizations.

DR. TUCKSON: But for right now then, you are on the yes side?

MS. MASNY: Yes.

DR. TUCKSON: Hunt?

DR. WILLARD: Just a point of clarification and correction for Joe. The profession of genetic counseling has been around for 20 years.

DR. TELFAIR: That was not my point. That was not what I was saying.

DR. WILLARD: But it was interpreted that way by some. Good.

I'm still where I was yesterday. I'm persuaded by the statement, particularly from James, that there is just not a base of evidence sitting in the literature that tells us yet, those of us who have done this on the front lines, that this is in fact a critically important field that is making a valuable contribution, and a contribution that is absolutely in the middle of the road in terms of how to bring genetic information to the public at large.

So I recognize that there is a gap, that the profession of genetic counseling is likely to be critical to filing that gap, and yet I don't see in the medical literature the data that would be necessary to make the case to the Secretary that in fact the drastic changes that

I think are needed will be needed soon.

So I'd have to vote no, but would then urge that we change some of the language to be much more forceful about the expected role that we see for the profession of genetic counseling as we go forward.

DR. TUCKSON: Okay. We'll come back to that, then. All right. I missed a hand here.

DR. FRIES: Yes. I just wanted to point out that while evidence-based medicine is a wonderful tool for all of us to evaluate our practices by, unfortunately evidence-based medicine does not apply to every medical practice that we do and that we reimburse for.

For example, there is not a lot of large randomized, blinded, control trials just about anything in genetics. So if we use that to drive our old policies, I think we are being premature in this. Much of medicine does not have that basis. That doesn't mean that it is not justifiably reimbursed.

DR. TUCKSON: Good. All right. Here is what we're going to do. I'm sorry. A comment?

DR. ROLLINS: I was just going to make a response to that. It is true that a lot of activities that we do in medicine, there have never been randomized clinical trials to show that they work. But that doesn't mean that observational studies were not performed.

You might even have to resort to such things as a cross-sectional study to use as an evidence base. But it is sort of like what David Eddy has said. Seventy percent of the things that we do in medicine have never been tested to see whether or not they work. We just do them because we think they work. Because of that, we tend to justify what we continue to do.

DR. TUCKSON: All right. This has been a very good discourse. Very rarely do we actually take votes on stuff, but right now I need to just sort of take a vote of the committee.

I wanted to have the ex officios who weighed in, I counted your votes, because first of all, you're valuable here, and it is important to hear you. You had a lot to say about this.

I want to see right now for the committee members that are here. Wait a minute. There are seven? Now, we had Debra. She clearly left. So does she count in the seven? I think she was pretty clear. There was no question about it.

MS. CARR: She makes eight.

DR. TUCKSON: She makes eight? All right. Of the eight committee members that are here, those members who are here who are voting yes, would you raise your hands?

(Show of hands.)

DR. TUCKSON: So we've got one, two, three, four. Okay. And those that are voting no, what do we have?

(Show of hands.)

DR. TUCKSON: One, two. So four to two. I'm trying hard to be diplomatic.

DR. FITZGERALD: I'm not a voting member yet. I haven't passed through the hoop of fire.

DR. TUCKSON: You actually would have tipped it more towards the five to two than the four to two, if I understand you correctly. So that's what that is, which is an important sense of the committee. So I think the committee has got a sense of it. That's where we are on the issue.

Now the question becomes how do we phrase the recommendation about how this would go forward? So now, let's specifically focus in on, and I'd like to put as the first way of focusing in on this would be, I'm looking for the greatest agreement possible.

I'm wondering whether that is around the language of the Secretary using leadership to expeditiously cause something to happen. I'm just trying that first to see where that takes me. Now everybody has got to get on board. We decided that we're going to make a

recommendation.

Now the question is how do you make that recommendation work? Who has got a thought there now about which of these options is the best way to make this recommendation happen? What is the most responsible way of getting this done?

DR. TELFAIR: Reed, a point of clarification before we get started.

DR. TUCKSON: Please.

DR. TELFAIR: Does the vote for yes negate the need to gather information independent of how it is done? There are varying ways. I agree with James that there is more than one way to gather information. I am just wondering whether those who voted yes, because that is not on the list.

DR. TUCKSON: The answer is that what I was trying to do by making that sort of point of departure now by saying the Secretary gets involved, and that all those sort of gathering the information things are the things that we urge the Secretary to cause to happen, is a way of trying to close the gap between the yes's and the no's.

Now, you can decide of course to do it a different way, but I was being fairly transparent, or trying to get everybody at least on a common next step. But it may not work. So please, who has a suggestion about

how now based on the things that are on the page and/or something new, about how do you achieve this.

It has got to be a specific recommendation, it has got to take us from Point A to Point B. We can't talk about the theory of it anymore.

DR. FRIES: I was going to ask Barbara specifically as a genetic counselor herself, what area does she feel would specifically benefit the field the most.

MS. HARRISON: I think a general recognition of genetic counseling as a legitimate field, legitimate service, is really what would be most helpful. I think everything after that will fall into place.

DR. TUCKSON: So you got that. That is already done by the vote. So now what do you do? How do you implement it? So let's be specific.

Do you say that everybody who is right now an certified ABGC or GNCC would be someone that we would urge the Secretary to, and go back to the language that Cindy said again, the Secretary for the government has got to urge Congress to say that if you have those degrees, those certifications, you should be able to go right in and do it now? Or do you say that you want the Secretary to cause the right people to be pulled together to give the best advice as quickly as possible to answer these questions about how to do it, and then take that to the Congress? Do

you take it as one step, or two steps?

MS. ZELLMER: Maybe I'm totally misunderstanding. I think the things on back about direct billing for prolonged services in the CPT codes, I think all are very important. All of the things on the front, to me, I'm not really sure. I think they affect licensure, which I don't think we would have any role over, or certification, which again, I don't know that it's that important that we have some kind of national certification.

Maybe I didn't get the point of yesterday. But I think that do we need to even go here? I mean, I agree with all of the recommendations on the back, but are any of these recommendations under yes, something we really want to do?

MS. HARRISON: I think the issue of licensure and certification, I agree, may not be an issue that we specifically have purview over. However, the main impetus behind us even getting into this is an access issue. It is an access issue, and it is a quality of care issue.

That's where I think the licensure and certification comes under. So we're trying to make sure that the people who bill for genetic counseling services are qualified to do so, and I think we agree as a committee that genetic counselors are qualified to do that, that nurses are trained are qualified to do that.

That is where I think the licensure and certification comes in. Mentioning licensure here is no more saying that the Secretary has purview over that no more than me mentioning certification here. I don't see why it has to be either licensure or certification.

DR. TUCKSON: Kimberly, the issue really just became one of, and you are raising an important option. It is to stay moot about it. The question is how do you make sense out of who is in fact a legitimately qualified person. Right now, there does not seem to be any real organization that allows you to figure that out.

MS. ZELLMER: I'm not convinced that 95 percent of the physicians who give advice on genetics are qualified. I don't really see this as an access issue. I think that it is important that you get information from qualified professionals, but I think that that issue is a totally different issue.

I think it deals with the broader medical profession in general. I don't think that we should limit it to say we've got to get qualified genetic counselors. I think we've got to get medical professionals who have a basic knowledge of genetics.

DR. TUCKSON: Good point.

Next?

DR. FITZGERALD: As far as the certification, I

mean, one way since you're talking about it, could there be multiple steps to this. We have certification processes, and the training and everything like that. Could you start by saying here is the starting point. Genetic counselors and nurses who have gone through the certification program are going to be accepted as certified. Now you need some group to come and look and see if, as Joe was mentioning yesterday, are there others that would be included under that umbrella?

I mean, I think you've got a starting point with the ABGC and the GNCC. Then you can see from there where you might want to go.

DR. TUCKSON: All right. This is a very specific recommendation. That's a very specific step. So if we understand it here, it is the idea.

Kimberly, I'm trying to figure out what to do. But again, at the end of the day, there is a sense by many people, there is a need to try to understand. If somebody is going to say, I am a qualified person and I therefore should be able to bill for this service, and I should be able to do this service and get reimbursed, any reasonable paying organization is going to say well, who are you? Under what criteria are you saying that you are in fact legitimate and able to do it?

You're right, Kimberly. Your point is that

you've got doctors and others who may not, but we're looking at this issue here. So the notion is that what we have as a specific suggestion is that you take the certifying bodies that exist today, and you say okay, this is a good starting point. Then you urge the Secretary, if I understand you, to create, or to try to use his influence to try to create or stimulate the formation of a body that would then deal with all the one offs that are going to come up, the single gene people, somebody without a Masters degree, who know who decides. I'm in the club, put me in the club. So somebody has got to figure that out.

You are asking for two things at once. Start one place, and then create an environment that figures out how to do it with all the people that are not in this group right now. That's a suggestion. So you've got something to shoot at. Now, let's decide. Is that the way to do it or not?

DR. TELFAIR: Can I just make a friendly amendment to this? I think it's important to take this suggestion if we're going to take it, and it be very clear about the nature of it.

There is a siloing of risk here. You need to eliminate that. If you're going to get groups to work together, it needs to be on common ground. So if we're directing or making a strong suggestion, then we need to

make sure that the group, whatever is formed, is a group that works towards the common ground in a collaborative way to make this happen. I just want to add that language.

DR. TUCKSON: That's a very important point. And by the way, I want to make the moderating comment that Cindy's point is I think very, very important in a realistic way.

This is going to be subject to a public discourse beyond our recommendation. So that I think what we're doing is we're signaling a direction. We are also signaling caveats that need to be carefully considered in the interim period while this goes through the public policy discourse.

Again, the Secretary cannot just with the stroke of a pen make any of this happen. So we are signaling things that ought to occur, and hopefully stimulating a lot of people in this room, and those that are on the webcast who are listening to this carefully, to create the details that are needed. So we're fast forwarding this whole field simply by the recommendations that we're making.

That is what I think is ultimately occurring in this room right now. Somebody's hand I missed. All right. Specifically, is Kevin's point the one that wins or not? Somebody has got to knock it down, because right now it is

gaining momentum.

DR. FEETHAM: I would just remind everybody of Barbara's comment. I mean, to me the three messages are the need for genetic counseling services, and we have been consistent on that language, by qualified providers who are of many disciplines.

The point of access, I mean, this bottom line, again, for the good of the American public, what are we talking about? Those are messages. By the way, to do this, we need reimbursement.

DR. TUCKSON: All right. Kevin has got it on a going, going, gone basis.

Agnes?

MS. MASNY: Well, I think that if we went with Kevin's recommendation, what would happen is that that would actually limit the number of health care providers that people would have access to. I think we want to make sure that people do have the access.

The main point that I think we're trying to continually get at is that the public needs access to qualified health care professionals, and that genetic counselors are qualified. They should have access to reimbursement.

DR. TUCKSON: Now, I'm not sure though, and I want to respect your point, even in rushing this thing

through. But I'm not sure that I see the limitation.

I think what Kevin is saying is you've got a place. You are signaling that we accept that there are some people who have created something that makes sense. Then he is saying expeditiously let's get to the process of how do you create the requirements, the conditions, and the processes that allow others to be designated. I don't see how that is diminutive.

MS. MASNY: Not diminutive, but in terms of limitations that we are now going to create another sort of more centralized body for certification.

DR. TUCKSON: Right. Now, the philosophy here, just to make sure that everybody is clear on this, is that you could then, the alternative, and I don't know whether this is what you have in mind. The alternative would seem to be that every organization with an interest in this could then certify, designate, and say okay, well, me, too.

So at some point, you are sort of left with if you are trying to pay for this, or you have to administer this or make use of this, or worry about a malpractice of this, it is like well, who are you? I mean, somebody somewhere along the line, and I think what he is saying is he has to make sense out of this so you don't have the wild, wild, west. I certainly don't want them coming to us.

DR. FRIES: It appears to me that there is some sort of a parallel for this in thinking about it in the capacity of certain physician skills. For example, if I am someone who wants to just simply do spinal surgery, I must first of all qualify as an orthopedist, and then perhaps do a subspecialty in spinal work, and then I only get to work on the sacrum.

I have made that my derivative. The same way for someone who is a single-disease counselor. That person must first of all qualify in the general capacity before they can then focus. So the point I'm trying to make is that there is an existent certification process for someone in general. If someone chooses to be in a very minor part of that practice, they must first achieve that, and that's already in place.

DR. TUCKSON: So what I think you're saying, for the purposes of this activity, is A, we are not trained, smart enough, or have the time to figure all that out. B, we know that somebody needs to figure it out, and we are urging the Secretary, therefore, to figure it out, or to use his influence to convene those that are necessary to figure this out.

DR. FRIES: That's sort of an overview of what I was commenting on. But the point that I'm saying is that there already exists sufficient certifications in place.

DR. TUCKSON: So those are models that might be used to apply to this activity. Or are you saying push this into existing forums that are already created to do this kind of work?

DR. FRIES: Certification in some field. For example, to become an OB/GYN doctor, I go through a board examined to certify. That's already set in place. Same process for genetic counseling.

Licensing, as we all know, is a state process. The reason I raised my question to Barbara was not that I think the Secretary has to do this, but whether that would be politically the most advantageous thing to the genetic counselors, or whoever is going to do it, to help them move forward.

DR. TUCKSON: All right. I saw one other hand. I want to do that. I missed you.

In fact, it was you, Kimberly.

MS. ZELLMER: The only question I had is whether this is really what the genetic counselors want. I think if they would like us to give the message to the Secretary that we need some national certification to make sure that people are qualified who are giving genetic counseling services, I'd be much more supportive of it.

But I guess I just would want to make sure that that is what they are interested in.

DR. TUCKSON: I guess the challenge we have there, and Kimberly, I appreciate that. We did hear wonderfully from the genetic counselors yesterday. They gave us good input. At some point I think the committee has to decide what it thinks it wants to do. We got a lot of input. We have differences of opinion even around our own table. So I appreciate the point.

The genetic counselors were able to express, if I can try to summarize what we heard, that they have their mechanism. There were a couple of organizations that spoke eloquently about what they do. Even in their own discourse, there were some issues that came up as to whether or not you only have Masters level nurses. They have their own challenges that they have to work through together.

What they did not do, and were not asked fairly, according to Agnes' point, they were not asked to, but they did not teach us about what to do with the single gene people and all the other permutations of issues. So we don't know quite what their guidance is on that point.

To conclude this. I'm trying to do a quantum calculus here to get your point in here. I can't figure out a way to do it, other than to simply say that I don't think that we can be more prescriptive than what we have gotten to.

I don't know whether it should be that this all goes and just gets pushed into the ABMS, which it can't, or something like that. At the end of the day, we can only do the best that we can in terms of this recommendation, and then let the process unfold as it needs to. We are making a pretty clear statement.

This is a bold statement, I think, to make, quite frankly, in terms of moving this field forward. One that is of concern to a couple of our members. So I think we have pushed this pretty far. I think what the next step is, and again, by the way, the other issue here is that the reimbursement committee report is going to go out for public comment, so we're going to get a whole lot of stuff back anyway. This is not the last time we're going to see this. We are probably going to get beat up on all sides. Then we'll have done our job wonderfully.

Cynthia?

MS. BERRY: Can I just make a recommendation that sort of builds on what Kevin had articulated? That is, following the model of registered dieticians, the way they got some coverage under Medicare for medical nutrition therapy for certain cases, I can't remember now whether it was diabetes or cardiovascular disease, but anyway, something like that, there were a couple of indications was that Congress put into the statute that the National

Academy of Sciences would conduct a study and look into many of the same issues that we have at the top of the back of this paper here dealing with cost-effectiveness, appropriateness, and all of that.

Then based on that study, and it was done, Congress looked at it and said, oh, for these two indications, it does make sense for these individuals to be able to directly bill Medicare for their services. Therefore, we will allow that to happen in those cases.

So what if our recommendation is asking the Secretary to direct NAS, or to fund some study mirroring, using the registered dietician model. That would be a next step closer. It would obviate the need really for Congress to step in initially and actually authorize the study. I mean, the Secretary theoretically could direct some funds that way, but it may ultimately be that Congress has to get involved. At least that would move the ball forward.

DR. TUCKSON: I would be surprised if there is anybody here under the reality that we've already moved the ball to the next step that wouldn't think that we don't want to wait for Congress to have to do that. I think your suggestion makes all the sense in the world.

Even those that were not in favor of the proposal were all in favor of expeditious. So I think you're talking about jump-starting that, and I think that

none of us would disagree that we wouldn't want to say okay, we've got to go to Congress and get permission to do the analysis. No. So I think your point wins the day. I don't see anybody rushing to disagree.

DR. FEETHAM: I would just like to remind everyone that HRSA and NIH funded a three-year beginning study on the genetic workforce, which was interdisciplinary, looking at specialists, non-specialists, and primary care providers. If we could build off of that excellence --

DR. TUCKSON: That helps. Cindy has that and needs to roll that in. Here is what we're going to do next. We're going to bring this to closure. Here is what happens. I need a reality check from Sarah and Cindy.

The reimbursement policy coverage thing has been kicking around now for a good while, and has gotten better every day with all the input. What is our timeline for when we absolutely expect and must have that report go out for public comment?

MS. BERRY: Can I ask one thing? I don't know how you want to handle it, whether you want to blow them off or what, but we have two remaining recommendations unrelated to genetic counseling. I think, and I don't want to jinx it, but they're probably in the no-brainer category where we might get some pretty quick consensus.

Do you want to turn to those?

DR. TUCKSON: I'll suspend it for just a second. Thank you. Thank God you raised it. But just for the moment, what is the timeline of when this report has to go out?

MS. CARR: Right away.

DR. TUCKSON: Right away is the answer. So in other words, I think what that means, and let me just make sure, does that mean, therefore, that the one thing we are not going to do is to put in the things that we've done today and yesterday, all the work that we've done, and then come back and revisit it at the next meeting? We are actually intending that it goes out before the next meeting?

MS. CARR: Well, let me just say, it's always up to you. If the committee doesn't feel that at the end of this meeting they are ready to go out with the report for public comment, we can wait until June. I mean, I think you want to do something. I think your goal was to have the report finished.

DR. TUCKSON: All right. Second question. Would you, Cindy, be willing, and again, you tell me about the process, that given how much work we did on that report this meeting, that the committee, subcommittee, redo a last draft on this, and then it will go out before June, but

giving folk if they have just any little comment they want to make, you can decide if we use it or not, but you can make sure everybody sees what it is going to be before it goes out for public comment.

Knowing again that going out for public comment means just that. It is not absolutely perfect. We're going to get some comments back, and then we'll come back and change it again. I think we're agreeing we're not going to wait until June to send it out.

The question I'm asking then specifically is would you object to having people at least send in some email comments on what will be now the last draft?

MS. BERRY: That will work.

DR. TUCKSON: That will work. Okay. With that, can anybody find their last two recommendations from yesterday? Those, by the way, who are public comment people, I hope none of you have to catch a plane, because we're coming to you, not too many minutes late.

MS. BERRY: The last two, it is on the summary document that was in everyone's folders. They deal with the broader issues.

Just to summarize the first one pertaining to provider education and training, it addresses the fact that there is a lot more work that needs to be done in making sure that the current medical workforce is adequately

schooled in genetics and genomics such that they can provide the requisite care to their patients.

So this recommendation essentially pulls from something that was recommended to the Secretary last year. You can read it. It basically asks the Secretary to develop a plan for HHS agencies to work with state, federal, and private organizations essentially to help medical professionals so that they have the tools they need. It also urges the Secretary to incorporate genetics and genomics into HHS initiatives. That's the first one with regard to education and training.

DR. TUCKSON: Does anybody have any big issues with that?

DR. WILLARD: I move we accept it.

DR. TUCKSON: Going? Going? Going?

(No response.)

DR. TUCKSON: Done. Next?

MS. BERRY: All right. The last one. Public awareness recognizes the lack of knowledge or complete information available to the public with regard to genetics and genomics. States the fact that we need to get out to the public reliable and trustworthy information about genetic technologies.

It talks about the development of performance and efficiency measures based upon evidence-based clinical

guidelines that would better enable consumers and patients to evaluate health plans and health providers.

Now, it's sort of vague and fuzzy. I don't know if we want to be more specific than that. It really doesn't say who will develop these things. It would be good to get some input from members of the committee as to what we might suggest here.

DR. WILLARD: This one doesn't actually read like a recommendation. It is just a statement of motherhood and apple pie, which is fine as a statement. That's actually in the text. We're not actually making a recommendation to have the Secretary do anything. So I'm not sure we actually need it. The text I think stands pretty well by itself.

DR. TUCKSON: Yes?

DR. KHOURY: The only thing that might apply to HHS is to provide direct recommendations about initiatives like the Surgeon General Family History Initiative, which is something that HHS is spearheading anyway to encourage, suggest, or whatever language you want to use.

By the way, if such a recommendation is changed, I would suggest to add the words "family history" somewhere.

DR. TUCKSON: Well, I think what this is getting at, I mean, I think everyone understands it, but

again, this is the consumerism movement where now people are having to make more choices that are financial risks for them about where they go for care, and the nature of the benefit packages that they are offered.

So what this is sort of getting at is saying I think what the recommendation would be, Hunt, is be more around the Secretary of Health making available through government Internet websites, information that helps a person make better and more informed choices in this regard.

Including family history would be part of it. So I'm one of the people that are addicted to the National Library of Medicine website.

DR. FITZGERALD: PubMed.

DR. TUCKSON: PubMed, that's it. So in other words, the Secretary would sort of help make sure that this kind of information was on a PubMed kind of site.

DR. WILLARD: But do we have enough information? At least I don't feel I have enough information to say whether that should be the Surgeon General's site, or it should be a CDC site, or any other site.

DR. KHOURY: It should not matter as far as this committee. You ask HHS to do it, and then we figure it out.

DR. TUCKSON: So you are saying use such resources to make this information available to the public. Guidance and education to the public. That is what this is getting at.

So with that as perhaps a friendly amendment, we would urge the Secretary to make HHS resources appropriately available to guide people in making these kinds of choices and decisions. Okay, done.

We are going to conclude this and move to the public comment. Let me just say this. Let me ask one favor of you in terms of the report that Cindy sends back out.

It would be this. Normally I'm not a big fan of people who if you send them an email to a multiple list, and then they've got to tell you yes and send it to everybody so that you've got 1,000 emails that don't make sense. In this case, I think it does make sense that if you make a comment on the report, you might want to click everybody, so everybody sees the comments that are going back and forth.

At the end of the day, Cindy and the committee have the responsibility for taking that stuff and weaving it into a final document. But I think in this case it is probably better that we all sort of share our thinking and thoughts. But you don't get to reargue the issue, that's

the only thing. The issue is resolved. Now the question is how do we do it?

You all are terrific. You guys are a terrific committee. Even when people don't agree, you work together. You are a model of democracy.

Public comment -- speaking of democracy -- Susan Manley, National Society of Genetic Counselors. I want you to sit right there. Head of the table. They'll make the microphone work.

MS. MANLEY: I thought this would be good timing. Good afternoon. I'm Susan Manley, Chair of the Professional Issues Committee within the National Society of Genetic Counselors.

As you know, NSGC represents over 2,000 member genetic counselors practicing in a variety of medical specialties, providing genetic counseling in prenatal, pediatric, and adult settings, as well as working in academia, research, and biotechnology companies.

NSGC would like to thank this committee for taking our previous testimonies and information into account when developing draft resolutions and reports, and we would like to continue to have input where appropriate as SACGHS moves forward with the important issues discussed at this meeting. Primarily billing and reimbursement for genetic counseling services and the development of

population-based genetic databases.

With regards to reimbursement and coverage issues, as you heard yesterday, genetic counselors are uniquely qualified to provide genetic counseling services. But without reimbursement for these services, the public's access to appropriate genetic services faces a limited future.

It is critical to note that Masters trained genetic counselors currently make up over 50 percent of practicing genetic specialists, which means that genetic counselors are currently providing the majority of genetic counseling services, and will likely continue to do so in the future.

Although additional studies must be done to clearly define the value and cost-effectiveness of genetic counseling services as conducted by specific providers, there are already many examples cited by the working group on genetic counseling services through invited testimony yesterday.

The issue of reimbursement for genetic counseling services and in particular, those provided by Masters level genetic counselors, is critical when we consider the impact on the genetics workforce. Specifically, if genetic counseling services provided by genetic counselors and other non-physician service

providers are not reimbursed, it will continue to impact access to quality services nationally.

This committee is in the position to make recommendations regarding the future of genetic services in health care. Currently, the educational and credentialing structure exists to produce quality, certified genetics professionals. However, without adequate reimbursement, public health could be compromised by the provision of increasingly available genetic services by uninformed health care providers without specialized training.

As was proposed yesterday by the working group, the NSGC appreciates the support of this committee, and strongly encourages you to continue to develop recommendations that explicitly support the recognition of non-physician genetic services providers, specifically including Masters trained genetic counselors who hold credentials that document knowledge in human genetics and clinical genetics expertise.

We also hope that SACGHS will advocate in all matters appropriate for the development of CPT coding that is specific to credentialed genetic counseling service providers, and for both third party payers and CMS to recognize the importance of reimbursement and coverage for genetic counseling services by appropriate providers.

Lastly, SACGHS can recommend that studies be

funded to continue to assess the value and cost-effectiveness of genetic counseling provided by non-physicians.

With reimbursement, qualified genetic counseling providers can become even more valuable in the financial realm of U.S. health care, and allow more medical facilities to offer quality genetic services to the public.

Finally, the National Society of Genetic Counselors applauds SACGHS for considering the logistical and ethical issues associated with large population-based genetic studies. Many of our members work in research genetic settings, functioning as research coordinators, including the provision of informed consent.

NSGC members recognize that the scientific data that arises from population-based studies will have a powerful impact on the data that is available to provide clinical information to patients in the future.

DR. TUCKSON: Thank you. Susan, that's terrific. I just would say that that's a very important statement. So now given where the committee is, I really, really hope, at least as the Chair of the committee, that your community now will take the initiative and really move forward and provide very detailed and very explicit suggestions into the public discourse around how you actually now accomplish this certification.

Not just for the small groups that have it. You've got to really figure out how that is going to work. You have heard us about 12 times say that there are some fundamental questions that need to be dealt with and answered. You guys have opinions about it, and you probably know others, but I think the ball is really now back in your court in your community to respect the professionalism of what you do and figure this thing out and make those suggestions.

I really appreciate your comments. As I say, now you threw it at us, and we ran with it. Now the question is you all are going to have a lot of work to do. I know that is what you wanted.

MS. MANLEY: And we know that already as well.

DR. TUCKSON: I figured that. Susan, you have been terrific. Thank you so much.

MS. MANLEY: Thank you.

DR. TUCKSON: Greg Rapp? Greg? I'm sorry. Please come right in and introduce yourself for the record.

MS. MENSH: My name is Stephanie Mensh. I'm a consultant to AdvaMed, the Advanced Medical Technology Association. AdvaMed represents manufacturers of diagnostic and genetic tests, among other medical devices, which is why we are interested in the activities of this committee.

We'd like to thank you first for the opportunity to make comments during this session. We're very pleased with the amount of time that you've spent deliberating on issues that our members consider to be very important relating to the coverage and reimbursement of genetic tests.

We do believe that for the tests themselves, how Medicare treats them will have an impact on access. We understand that there are certain limitations in terms of prevention and information in how the agency views these tests, and what they are used for.

We do appreciate the amount of time and effort that this committee has put into understanding the issues. Hopefully your report will be a major source of support to move this forward through Medicare and other agencies that are related.

We did submit specific comments, almost line by line comments in September, and appreciate how much work has been done since then on the draft. We do look forward to doing a very careful review of the report when it comes out for public comment in the next few months.

What I passed around is AdvaMed's policy statement on another section of the Medicare Modernization Act, which we hope that you'll also address in your report, even if it is just to acknowledge to CMS that you are

interested in how they are implementing this section of the report. It has to do with how new tests are paid under the clinical lab fee schedule.

You did mention the MMA provision having to do with coverage in the report, but this is Section 942. It also talks about the disposition of new tests. It puts into place a very thoughtful process. A public, open, transparent process. We think this is important because we would like to be sure that the agency and the contractors in the field who may be doing gap filling understand completely what is required of them to develop cost data for new tests, and that this information, the data is made public.

AdvaMed has summarized what is in the law itself at the beginning of the policy statement, but also because the statute is fairly broad as it is written, we have offered our suggestions for additional regulatory provisions that we believe can be implemented on the regulatory level.

There was an open meeting, a town hall meeting, that CMS held in January to take comments. We provided our comments to CMS at that time on new tests, on implementing this section. It is our understanding that a notice of proposed regulation will come out in late spring or early summer to implement these provisions. So the timing of

your final report will be right on time if you were to just mention that you are interested in how CMS is carrying out this provision of the law.

I think that that is pretty much what we're asking for, is to just have your recognition that these provisions are important, and that some stakeholders, like AdvaMed and others, in the lab community are very interested in being able to have the best that we can get for new tests, understanding the limits of the current Medicare fee schedule.

Again, thank you for this opportunity to comment. We hope that you will consider making a recommendation in your final report that relates to implementing the new test section as well.

Thank you.

DR. TUCKSON: Thank you very much. Let me also thank you all for a very well done briefing paper. One page, front and back. Very specific, absolutely right to the point on every point you're making. We understand the point that you're making very clearly. Obviously a lot of work went into this. I think it stands on its own. We have this, and we will certainly study it.

Does anybody have a question?

(No response.)

DR. TUCKSON: Again, very well done. Thank you

very much.

MS. MENSH: Thank you.

DR. TUCKSON: Maureen Smith from NUgene Project, Center for Genetic Medicine, Northwestern University.

MS. SMITH: Good afternoon. I'd like to take us back to the topic from this morning on large population studies. I represent the NUgene project, which is a genetic banking study conducted at Northwestern University in Chicago, Illinois. The NUgene project is a population-based initiative whose purpose is to develop a diverse collection of samples and information that will facilitate biomedical research on the genetic and environmental factors contributing to health and disease.

NUgene currently combines a centralized genomic DNA sample collection and storage system with the ability to regularly update participant's health status and retrospective and prospective data from electronic medical records. The project received initial seed funding from the Northwestern University and its health care partners.

I will shorten my statements, as this has been fairly extensively discussed this morning. I just wanted to make a few points.

One is the NUgene study is conducted throughout the Northwestern Health Care System, which includes five

hospitals and numerous outpatient clinical sites throughout the Chicago area. We are an approved IRB study through the Northwestern University IRB, and we have a certificate of confidentiality from the NIH.

I did want to point out that we have spent time since the inception of this study in early 2002, up until the present time, and continue to work very closely with our IRB. It has been a very lengthy process of education and work, so I wanted to point out that I think it does take a huge effort to educate IRBs about this type of research.

Our recruitment began in late November 2002, and we had very modest initial accrual goals so that we might better understand how to best educate and work with our physician and participant populations, as well as to evaluate how to improve recruitment in our informed consenting processes.

We have found people to be responsive to learning about the study, and agreeing to participate. However, that certainly does vary given the situation in which participants are approached. But while the public appears interested in participation in studies of this type, we are aware of the need to continuously examine the ethical, legal, and social issues associated with acquiring, maintaining, and managing personal health and

genetic information as a large resource.

Therefore, we recently served as the site for the Department of Energy-funded ELSI study of informed consent for population-based genetic research. This project assessed the participant knowledge of our study with the goal of improving the informed consent process for large population research. Results of this study have been presented at scientific meetings, and we are in the process of publishing that data.

The longitudinal and population-based design of this study positions NUgene, as well as similar studies, to be a resource for a breadth of studies, and I won't go into those, as they were extensively discussed this morning.

We believe that our project has begun to demonstrate the value of such collections for research, as over the past six months, being even a small population study, we have distributed samples for three different research studies within our university. These investigations included such varied and common conditions as aneurisms, neural tube defects, and head, neck, and lung cancer.

In conclusion, we believe that large population studies will offer great benefits to society, and will enhance our understanding of how environment, lifestyle, genetic, and other factors contribute to health and

disease. The experiences and expertise of existing population studies in the U.S., particularly in the areas of informed consent, building sophisticated data management, and sample storage systems, developing privacy policies, and establishing community trust can be leveraged to provide a framework and guidelines for further studies.

As others in the international community work to create country-specific, longitudinal population cohorts, we believe that preexisting U.S.-based population repositories should be further developed into a national, not-for-profit consortium.

DR. TUCKSON: Well, thank you very much, Maureen, for that. Also thank you for letting us know that the NUgene project is available as a resource as we look forward to these issues going forward. I know several of us will probably try to take advantage of that. Thanks for taking the time to make sure that we know what you are doing.

MS. SMITH: Thank you.

DR. TUCKSON: We appreciate it.

Finally, Mary Steele Williams, the Association of Molecular Pathology. Welcome.

MS. WILLIAMS: Thank you. I'll need to provide a new written document to Sarah based on yesterday's discussions. The verbal comments are a little bit

different from the document that I provided you with earlier.

Dr. Tuckson, members of the committee, good afternoon. My name is Mary Williams, and I am the Director of Scientific Programs of the Association for Molecular Pathology. I speak to you today as a representative of AMP.

The Association for Molecular Pathology is an international not-for-profit educational society representing over 1,200 physicians, doctoral scientists, and other professionals who perform molecular and genetic testing, as well as other tests based on nucleic acid technology.

The AMP membership is from a wide variety of health care settings, both public and private, as well as from the IVD industry. AMP members are involved in every aspect of genetic testing, research, and education.

My purpose today is to provide comments on several issues currently under consideration by the SACGHS. First, review of molecular CPT code reimbursement. AMP strongly supports the proposal in the coverage and reimbursement document to request CMS to review and revise reimbursement for molecular CPT codes.

As the number of available genetic tests and their use in routine diagnostics grows, laboratories will

not be able to continue absorbing the losses associated with genetic testing as they do today. We strongly support the SACGHS recommendation for CMS to review and revise reimbursement for molecular CPT codes. AMP, through its resources and knowledge of this subject, stands ready to assist CMS in carrying out this recommendation.

Second, change in the definition of a genetic test. AMP's position remains in strong support of the limitation in the definition of a genetic test to inheritable germline variations, and not including somatic variations. If a genetic test is more broadly defined as any molecular biology-based test, then there needs to be a distinction that allows for the discussion of the ethical, social, and regulatory issues to inheritable genetic tests separate from testing for somatic mutations.

This distinction is not relevant to the coverage and reimbursement report, but may be relevant to future reports of the SACGHS.

Third, better coverage and reimbursement for genetic counseling services. AMP in performing genetic tests works closely with genetic counselors and medical geneticists. These professionals provide essential genetic services to patients and their families that are time intensive, and are not adequately reimbursed. AMP strongly supports a recommendation to define genetic counselors as

allied health professionals allowed to direct bill, and to review the billing codes associated with genetic counseling services.

Last, gene patents. AMP asks that SACGHS give full consideration the negative impact of exclusive licensing and enforcement practices for gene patents on the future of genetic testing. We understand that SACGHS has set this as a high priority, but has decided to wait for the National Academy of Sciences' study of intellectual property related to genomics and proteomics.

We urge you to promptly set this as an agenda for the SACGHS as soon as the report is available. On behalf of AMP, I thank you for the opportunity to speak with you today. AMP remains available to the SACGHS to assist with or provide information for your thoughtful deliberations and important work.

DR. TUCKSON: Mary, thank you very much. Thanks for making sure that we are staying closely connected with the association. That's important that you are clearly with us as we go forward.

The patent thing we talked about yesterday, and we are right on board there. We are waiting for the NAS report as well.

We don't have a lot of time, but I just wanted to note in terms of I appreciated the guidance around the

laboratory testing thing. I'm not sure what we might do with that comment right now, other than we'll take it as you've made a point. We have to deal with it at some point. So we'll probably get back to it.

Thank you. Good job.

We're going to move forward and invite Dr. Joseph Boone, Assistant Director for Science, Division of Laboratory Services, CDC, and Steve Groft, Director of NIH Office of Rare Diseases, as they help us to look at the issue of the summary report from the Conference on Promoting Quality Laboratory Testing for Rare Diseases. You will remember that they had this conference in Atlanta in May of '04. They are making plans for a second conference. The executive summary of the proceedings is in Tab 5 of the briefing book.

While the conference was conceived as a plan to address access in quality of laboratory testing issues for rare genetic diseases or conditions, it wound up identifying a number of issues beyond the quality assurance. The group soon expanded the conference to include other topics of interest, many of which intersect with the interest of this committee. Therefore, we will be learning about that and seeing how it dovetails with our activity.

Thanks a lot, Joe.

DR. BOONE: Thanks very much.

It is unfortunate that Dr. McCabe is not here, because some of the things that we're going to be presenting are certainly relevant to this precursor of this committee. We are really addressing some of the issues that have been raised before. Particularly the issue of translation of research findings in clinical practice, and the issue of access in quality of laboratory services.

As Dr. Tuckson mentioned, we did have a conference in May of 2004. That conference did address primarily a set of issues that was raised by this committee previously. It has partners, Emory University, NIH, and CDC. That's the reason that we're doing this tag team presentation today.

Our definition of quality was really in terms of CLIA. We felt like at least the minimum requirements should be a certified laboratory. So the two areas where we were most concerned were research-only laboratories, and those laboratories that are located outside of the U.S., and the quality of the services that they might be providing to U.S. citizens.

So the basic things that we were looking at was to ensure the quality of access testing, and we were concerned about the research laboratories that might be providing patient testing without a CLIA certificate. We

were also concerned about the translation of gene findings in clinical practice. We had a number of other issues that were concerned about.

You have these charts in your books, but the main thing is that in terms of the U.S., 78 percent of the tests are being done in the U.S., 22 percent are being sent outside of the country, and 33 percent of the testing on gene tests are for research-only laboratories. That's the test themselves.

If you look at the distribution of laboratories, research-only laboratories account for about 40 percent of the U.S. laboratories in GeneTests. Non-U.S. laboratories count for 30 percent of all the labs listed in the directory. That was in 2004. The data haven't changed very much since that time.

Another thing that's important to look at real quickly is the fact that of the things that are tested for, many of those tests are available from only one laboratory, or from a very small number of laboratories, which makes some of the quality assurance practices that we'd like to have in place difficult to do.

There are very few tests that are actually available through the College of American Pathology survey program. Similar in Europe, there are very few tests that are actually being monitored in a quality assurance mode.

So in the summary slide, I think the main thing to focus on here is the fact that we're falling further and further behind in terms of development of GeneTests. Rare disease associations are being found at the rate of about 20 per month. The new testing that we are able to incorporate is about ten per month. So we're running 50 percent behind in terms of developing new tests to address the conditions that are being found in the gene findings. That gap really does need to be closed.

So the results of our first conference was that we actually formed a North American Laboratory Network for Rare Disease Genetic Testing. That network is comprised of laboratories that are all CLIA certified, and will report the limitations of the tests in their reports. They are going to work collectively to increase the development of new tests to foster research and clinical laboratory partnerships and serve as a back-up resource for additional tests.

There was an organizational meeting, which Steve is going to talk to you about in a moment. But there were about six laboratories that formed this original alliance of testing laboratories.

In addition, the American Society of Human Genetics and the Office of Research Protections agreed to provide education to researchers and IRBs, which is

something that was really needed. NIH has a pilot program to fund translation of research tests into clinical, applicable tests. That program, we want to see that expanded in a logical manner. Then we plan to have a meeting later this year, which Steve will tell you a little bit about.

So we're on a pathway I think that is the right pathway. We're not confused. We know where we're going. Steve is going to tell you a little bit about how we might get there.

DR. GROFT: Thank you very much, Joe.

You saw the stop lights, red lights, green lights, yellow lights. Sometimes I think we're working all at one time, so we're not sure how we're going to get there. As you will see in the last slide in the presentation, that's even more of the confusion that we're adding into the situation. I'll try to get this moving.

We do have a meeting planned on March 17th prior to the American College of Medical Genetics to really start to crystalize and finalize many of the discussions that have been held previously, both at the meeting last year in May at the Centers for Disease Control in Emory University in Atlanta. A number of discussions have been held by a lot of participants since then to look at presenting this at the September, 2005 conference here in

Washington.

We have been working on identifying major issues in target audiences that need to be at the meeting in September. We'll be looking at the conference agenda, and then assure that there is broad based participation in the meeting in September. We still are in the planning stages, but things are coming together rather nicely.

It seems like for the first time we've been able to get many of the major participants who we had to get together to really affect an effort that would have some outcomes that could move forward. We are getting together here finally, so it's good to see.

At the conference in September, again, it will be in Washington. It will be a two-day session. We'll have plenary sessions and reviews. And again, we're working all of these issues up that Joe had talked about as far as the vision and other things that we need to discuss to give us direction, movement, and the momentum to move forward.

A couple of the issues that we need to work on are trying to establish the priorities for developing genetic tests for rare diseases. There are so many disorders that we could look at and really start to work on. We really have to try to identify those priorities and the criteria for selecting them. It is just an area that

we hope to hear from a lot of people on how we're going to go about this.

The conditions for the clinical laboratory participation. We currently at the Office of Rare Diseases have a small program with the National Human Genome Research Institute within the Clinical Center to develop these genetic tests for about four rare disorders last year that we did under the direction of Bill Gault, the Clinical Director for the Human Genome Research Institute.

This year, we hope to expand that to about 16 to maybe 20 more tests that we will develop, mostly for the use of the Intramural Research Program. So we wanted to go forth and start in the intramural program, get some direction, some experiences, and then move possibly into the extramural program.

As we were moving forward last year in developing these genetic tests, we came to the conclusion that this was something that is quite capable of being done in the extramural program. Now we are looking for partnerships within the NIH system to expand the whole program to increase the number of genetic tests that are developed for rare disorders.

When you have a total of 6,000 or 7,000 rare diseases, it is quite a task. Where do you start? How do you continue? How do you gain the interest? But there

certainly has been a lot of interest in seeing this move forward to have the tests move out of the research stage into the stage of clinical accessibility for the public.

The next three slides that you have and that are available for anyone who may be looking in through the website, is we've talked about the long-term visions and the short-term visions for what we want to accomplish, and where we want to go, so I won't spend too much time on that. I know the day is drawing to a close, and people have their planes.

There are a number of areas that we want to talk about, and we will discuss the successes. How are we going to measure it? How are we going to identify the successes for the patient's families and the providers, as well as the laboratories and the testing groups. Then finally the success of the system and the services that will provide these services to the public.

We hope to evaluate whatever success we're able to achieve through pre and post-surveys of the laboratories, the consumers and advocacy groups, the Centers for Medicare and Medicaid Services, and other payers, and then to monitor the tests that will become available, and to monitor the quality of these tests, as well as any adverse events that may occur. That seems to be a major concern these days, as they should be.

Then we hope to lift the roadblocks and to remove them to create the models that will generate the energy to move forward towards the solutions. Again, we know there is a lot of passion involving individual rare diseases, but I think we have to look at this in the sense that we are not going to be able to do all rare diseases at one time. We will start in a systematic fashion and continue to move through and to complete as many as are possible at the present time currently that are in the research stage or in the research laboratories.

I guess we have been hearing about the need to do this for many years from a lot of the patient advocacy groups who of course would like to have a genetic test available for their disorder.

There is always the concern that if they are available from a research laboratory, that the research money will dry up, and the project will just die. It may never be available for use in the clinical services. So I think those are some of the areas that we're looking at, and some of the needs that we're trying to work with as we move forward.

This is a slide that we have tried to put together. We could have put all those different lights in there too as well. You see the number of partners that we are dealing with. Actually it has been very nice progress

I think as we move forward from the planning last year for the May meeting in Atlanta to where we are today.

The number of groups that are involved are numerous, yet there has been a good sense of a need to move forward quickly and as expeditiously as possible. So I think we'll just end it with that one and try to answer any of your questions that you might have.

DR. TUCKSON: Thank you both. Very, very important work.

The floor is open. Any questions?

DR. WILLARD: Just a point of information. Are there precedents or other examples where HHS steps in to prioritize development of tests for diseases that affect, by definition in this case, a very, very small number of its citizens?

DR. GROFT: I don't know of any directly, although looking back on when we started with the Orphan Drug Act back in 1983, we tried to identify compounds that were available on the shelves of companies that weren't being developed.

We tried to provide incentives. That's what happened through the Orphan Drug Act, incentives. But we also tried to identify compounds that would be useful. We went about then funding research, trying to support research for those areas.

So I think the scientists, the laboratory people will identify those. As I mentioned, some of the first areas we'd like to work with are those that are already in the research laboratories, and maybe could move over to the clinical side.

DR. BOONE: And we've talked about the federal process, but we also have a private sector process that's engaged in this overall activity with us. There were some 50 people that were at our original meeting, and we hope to have maybe as many as a couple hundred people at the September meeting.

We get the same message from the people in the private sector, that the rare disease community is coming to them with funds in hand wanting tests developed. They simply don't have enough capacity to move these tests through the system.

DR. GROFT: And for the most part, we probably will not establish the priorities completely. I think this is where a community will come forward. We are looking for a cooperative effort among the patient advocacy groups, the laboratories, the NIH, the CDC, and all of the government agencies who have to work together on this issue.

So there will be a lot of people coming together. In the last slide, you could point there as to who is going to bring the tests, the need for certain

tests, and everyone will be bringing the tests forward to us for consideration. But we will not be the sole source of funding.

MS. ZELLMER: I just had a quick question. Just based on what you said then, are primarily then the barriers to getting these tests developed the laboratories just not having the capabilities? Or are they more financial? Or both?

DR. BOONE: It's a little of both. I mean, Dr. Ledbetter at Emory University indicates of course there is enough capacity to do these tests within the United States, but some tests are going abroad. You have to ask the question, why is that occurring. I think there are several reasons that that is occurring.

I really applaud NIH for taking this initiative to try to put the researcher with the clinical lab in a partnership so that that transition period hopefully will take less time, and we'll be able to move tests more rapidly through.

This really is a network that is starting to build, too, because there are a few labs that are in this. If the pilot really works well, then certainly we can engage I think more genetic testing laboratories in this process.

DR. GROFT: I think with so many rare

disorders, there are so many possible conditions and situations that exist that you can't say it's this or that. There are many, many different possibilities here.

But we are hoping to have some pilot projects involving different laboratories so we gain the experiences of commercial laboratories, as well as CLIA-certified laboratories, some that are in so-called ultra-orphan disorders with a very, very small prevalence of diseases that we'll look at to see how things are done and how we might be able to just use those experiences to extend out to the entire community.

DR. TUCKSON: Thank you both. We very much appreciate it. We look forward to updates after the meeting. Thank you both.

All right. We are just going to have a couple of minutes, and then we know that some of you really need to get out of here, so we're going to end a little early, I think.

Let me summarize a couple of things I think that we said that we would do. This is not going to come out real well, because I thought I was going to have a few more minutes to actually sort of organize this.

Anyway, the main thing is that Sarah knows what we're supposed to do. On the genetic discrimination discussion, before you go, Muin, because there is something

that says you were supposed to do something. On the genetic discrimination, we are going to do the DVD. I did that narration this morning. So we have approved the script, and that is moving forward.

The public comments to the Secretary are being collected, and those will go forward to the Secretary. The legal analysis, we are not going to wait for the legal analysis to get done. But in the body of the letter to the Secretary, we are going to urge the Secretary to use all of his influence to expedite the legal analysis from the various departments and everyone that is involved with that. Then we are requesting that the Secretary hold the stakeholder meeting to help broker any differences that may exist in that community to move that forward. So those are the things that we agreed to on the genetic discrimination.

On the health informatics infrastructure, I think we wanted to send a letter to Brailer saying thank you, and urging again that we want them to remember what we are trying to do here, the family history issues in genetics being important as he unveiled his strategic plan. Muin is to work with Alan Guttmacher and/or Frances to draft the letter in fact to Brailer.

That's what you're doing. You already did it.

DR. KHOURY: No, actually, we talked with Alan yesterday. So I think Alan is taking the lead on behalf of

all of us, and we'll contribute.

DR. LESHAN: We'll work with you.

DR. TUCKSON: Oh, it's the old wait for Alan to leave, and then give him the assignment. That will teach you all to leave.

For whatever the Rodney Howell committee, what is it called?

MS. CARR: Heritable Disorders.

DR. TUCKSON: Heritable Disorders. Any of you that have comments that you want reflected there, go to Joe so that Joe Telfair can carry the water for us on that committee.

On the reimbursement, I'm not going to summarize that again. If you all didn't get that the last time, shame on you. So I want to also just -- large pop?

MS. CARR: Yes. On large population studies, we are writing a letter to the Secretary with a number of points that we're going to make.

DR. TUCKSON: All right. So we've got the large pop. That's exactly right. So we've got that. That's in our notes.

I want to welcome again to the committee Joe Telfair. I thought Joe was terrific. What a terrific addition to the committee.

Kevin, we'll just wait for him to leave, and

then we'll say nice things about him.

(Laughter.)

DR. TUCKSON: But Kevin, really welcome.

I just think this is really fun. What a good group.

I think all of you would join me, by the way, and the ex officios, thank you all very much for coming, and all the contributions that the ex officios made. It is terrific.

The webcast people, thank you all for that. Again, there are a lot of people out there that care about this. So thank you for that.

Thanks to the soundman. You were terrific keeping us on track.

Sarah and the team, always just stellar behind the scenes. Every single person is to be commended.

(Applause.)

DR. TUCKSON: Now, the people that deserve the biggest applause are the audience. I mean, how they can sit through this stuff?

(Applause.)

DR. TUCKSON: And they don't get to talk and just have to be talked at. But we really appreciate your involvement and expertise.

Does any member of the committee have any last

words?

MS. HARRISON: I have one last comment. I think I always say this at the end of the meeting. I still want to at least keep in our minds that we do have a duty to the public to let them know about our proceedings and things that are going on, and that the Federal Register may not be the best place. So I think we still have a duty.

DR. TUCKSON: Which I'll piggyback on also. Again, that comment that I made at the beginning of the meeting, I still want us to somehow, even though we've got a lot on our plate, how do we get at this education of the American public? Not just even about, although it is important what you are saying, it stands on its own about what we are doing, but it is educating the public around these issues.

I think that's important. I'm glad we got it into the recommendation at the end for the Secretary on the coverage and reimbursement issue, where we can start to get the Secretary using the information distribution mechanisms at his disposal to try to educate people about these things. I think that's important, so I'm just piggybacking on that.

Does anybody else have a comment?

(No response.)

DR. TUCKSON: Well, with that, it was a hard

two days. Good for you all. Thanks a lot.

(Whereupon, at 3:47 p.m., the meeting was adjourned.)