

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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Call to Order

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SACGHS Chair

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Professor of Internal Medicine,
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University of Montreal

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

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

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

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

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

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

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

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

1 genome.

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

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

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

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

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

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

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

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

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

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

1 basis for large population studies.

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

8 But kicking it right off, why we would want to
9 set up a powerful framework for studying the genetics of
10 common diseases, the basic motivations are indicated there.

11 We would like to be able to predict risk, but importantly,
12 and I'm going to come back to this a few times, we would
13 like to be able to not only predict risk, but do something
14 about it. It's not really good enough just to predict
15 risk. This is not for insurance companies. It's not good
16 enough just to predict. We have to be able to intervene.
17 So that's something that's going to up, I think, in a few
18 places.

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

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

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

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

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

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

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

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

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

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

1 isn't really appropriate to talk about genes for diseases.

2 We're not doing the same thing as we did with Mendelian
3 disease. We're finding the gene for diabetes and the gene
4 for asthma and so on. We are understanding on how genetic
5 differences influence these conditions. So its a different
6 kind of thing.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 This just indicates the way that this sort of

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 So common variation can be efficiently

1 represented. We should view that as non-controversial.

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

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

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

1 doubt lead to advances.

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

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

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

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

1 things about why they had a heart attack when they were 66?

2 And we don't know exactly what we should be looking at
3 when we enroll individuals for cardiovascular disease or
4 for other things. We really don't know.

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

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

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

25 That is basically not being done in epilepsy

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

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

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

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

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

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

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

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

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

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

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

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

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

1 polymorphism is in fact a risk factor.

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

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

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

25 So I'd just close by saying that when you

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

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

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

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

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

3 Thanks.

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

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

8 (No response.)

9 DR. TUCKSON: David, thank you very much.

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

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

18 DR. OMENN: Thank you very much, Reed.

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

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

3 So here is a visual image which actually is a
4 short-term vision, but we'll carry on for decades of work.

5 As you've just heard from Dr. Goldstein, we already have
6 the beginnings of an avalanche of genomic and genetic
7 information, validated SNPs, the beginnings of a haplotype
8 map for applications, candidate genes and alleles, and
9 especially many candidate genes and alleles for particular
10 disease risks.

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

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

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

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

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

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

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

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

24 (Show of hands.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

23 So this is a rich data resource. Over the
24 years, the NHANES II, which concluded in the '80s and had
25 14,000 people. NHANES III, 34,000 people. I actually

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

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

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

1 to actual bioburden measures of the sorts that NHANES does.

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

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

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

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

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

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

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

19 GIS I've mentioned.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 Statistical power estimates. It's very
21 important in planning studies, of course. They expect over
22 5,000 cases per year for diabetes mellitus, ischemic heart
23 disease, myocardial infarction, colorectal cancer and
24 breast cancer, and you can see here the projected relative
25 risks and interaction ratios that they would be able to

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 integrating the molecular information.

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

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

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

1 scientists disagree.

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

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

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

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

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

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

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

25 Finally, I want to point out some good work

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

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

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

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

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

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

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

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

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

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

25 I added this line on the bottom, which is that

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

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

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

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

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

8 Thank you very much.

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

11 Again, any one particular question?

12 (No response.)

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

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

18 DR. MANOLIO: Great. Thank you very much.

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

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

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

5 There are, as I said, a large number of these.

6 There are new ones sort of cropping up every day. Very
7 few of them had actually gotten into the field and gotten
8 going.

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

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

1 Japanese researchers.

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

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

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

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

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

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

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

10 The National Children's Study Dr. Brenner will
11 be talking about a little bit later. It's to include
12 100,000 infants and their mothers and to follow them for 21
13 years.

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

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

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

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

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

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

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

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

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

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

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

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

16 There is a non-profit Estonian Genome Project
17 Foundation which is in public/private partnership with
18 eGene, Inc., which was a private arm. Actually, they have
19 just recently dissolved their arrangement with eGene in
20 2004 and they're now looking for other sources of funding.

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

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

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

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

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

1 diseases.

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

11 They also have an extensive genealogic database
12 extending back to the settlement of the island in 900 A.D.

13 They have a very small number of high quality referral
14 hospitals and very good records.

15 DeCODE currently has DNA and data on 110,000
16 consenting Icelanders and about 25,000 non-Icelanders from
17 various parts of Europe that they have collaborations with.

18 It was begun in 1998.

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

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

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

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

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

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

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

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

13 This is actually the genealogy of Kar
14 Steffenson, who is the founder of deCODE, and he can go
15 into this, as can any Icelander, and trace his genealogy
16 back one, two, three, four, five, six generations to this
17 person. Then click on this next button, and she was born
18 in 1776, and trace her back another six generations. Then
19 the next one, born in the 16th Century, and in the 14th
20 Century, and in the 12th Century, and finally back into the
21 10th Century. So back to their original Norwegian
22 founders. Most of them can do this. It's really quite
23 remarkable.

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

1 database --

2 (Laughter.)

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

9 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 Disadvantages are that they rely on recall or

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

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

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

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

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

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

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

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

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

24 (No response.)

25 DR. TUCKSON: Well, thank you for that.

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

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

8 See you at 10:20.

9 (Recess.)

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

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

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

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

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

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

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

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

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

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

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

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

1 appropriate wording.

2 Also I will focus in this presentation on
3 really the new reality of human genetic research databases,
4 meaning large-scale population databases including at least
5 10,000 individuals.

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

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

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

25 Here you have a few countries that have

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

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

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

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

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

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

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

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

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

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

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

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

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

1 the specificity of human genetic research databases.

2 Again, we can no longer use the traditional consent models.

3 I don't think it's appropriate, neither for participants,
4 nor for the researchers.

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

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

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

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

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

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

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

25 The status of genetic material. Ownership.

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

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

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

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

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

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

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

10 Now, is Parliament the most appropriate way?
11 Or is it the appropriate democratic forum by which you
12 could engage the public and make sure that there is
13 legitimacy there? The question that we had is if there is
14 not enough public consultation, public communication prior
15 to this Parliament enactment of the legislation, we might
16 have questions with respect to the process. But
17 nevertheless, in many countries, at least it is very clear.

18 Whenever there is a legislation, you know the rules, and
19 you know what is being done.

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

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

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

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

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

25 Ensure data collector's participation and

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

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

16 Individual feedback and general results.
17 Again, that is something that the research team will have
18 to make a decision about. You see here different options.
19 In Estonia, they chose to really respect the right to know
20 in a way, and in other projects, there will be no research
21 results except for the medical examination from the start.

22 So that's another element you'll need to consider.

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

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

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

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

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

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

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

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

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

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

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

25 Public Population Project in Genomics is a non

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

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

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

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

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

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

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

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

1 Thank you very much.

2 DR. TUCKSON: Thank you very much, Mylene.

3 That was terrific on its own merit, but even more terrific
4 for having stepped in at the last second.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 out etiology.

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

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

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

19 What you do see, again, is that this is clearly
20 her disparity issue among people who have African ancestry.

21 About 14 percent here, about 34 percent here. You do see
22 a dramatic increase in body mass index. So clearly how
23 heavy you are and the environment where you find yourself
24 has serious implications for hypertension.

25 This is a new study that is extremely important

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 is confused with more complex ancestry.

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

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

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

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

1 different ancestry if you really go into the history.

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

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

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

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

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

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

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

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

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

25 But again, this shows that depending on the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 effort.

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

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

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

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

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

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

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

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

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

1 patient. I think David Goldstein made this point earlier.

2 The idea then is not to eradicate or ignore differences,
3 but to redefine or move beyond social group labels such as
4 (inaudible) to more precise categories of differences with
5 justification for establishing such differences.

6 Thank you very much.

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

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

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

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

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

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

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

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

16 This is John Solstun from Cambridge. He had a
17 role alongside many international colleagues in the Human
18 Genome Project.

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

25 But there is also I think a moral and political

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

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

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

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

25 So what we have to do in the challenges to make

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

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

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

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

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

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

9 This is part of a general trend in epidemiology
10 and clinical trials. These are just some of the studies in
11 the U.K. showing how many people were recruited, from
12 20,000 up to 120,000. So there is a general trend to
13 recruit more and more people at baseline. In the U.K., we
14 have the million women study which successfully recruited
15 in fact, at one point, 2 million people. They overshot,
16 they tried to stop at about 900,000, and ended up with 1.2
17 million.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 on people's health as they get older.

2 There are similar numbers for the numbers of
3 people who would develop instant illness in the future.
4 Gil talked about ten years. In fact, we plan to study
5 people indefinitely. So we are talking now about 10, 20,
6 30 years. At 20 years, we will have 86,000 people who have
7 developed coronary heart disease who didn't have it at
8 baseline. These are the sorts of numbers that you need if
9 you're really going to get to grips with the interesting
10 questions.

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

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

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

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

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

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

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

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

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

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

1 relationships might be.

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

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

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

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

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

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

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

16 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

1 of line.

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

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

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

18 Of course, box number five is very important.
19 It is always easy to forget this. In the end, the resource
20 is only as good as the extent to which you can distribute
21 and make available the data and the samples for future use.

22 It is important to put resources into that now as well.

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

1 questionnaire, the samples, how the samples are stored, and
2 the quality assurance data. At the end, we have
3 information coming in from the NHS particularly, but also
4 research input as well from dedicated follow-up procedures.

5 The whole lot has to be amalgamated in a secure database.

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

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

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

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

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

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

1 This is a system where the tubes, you'll see in
2 a moment, are stored in racks in here. These are held at
3 -80 degrees. The robot operates at -20 degrees. This is a
4 mock working factory, but it is very similar to the one
5 that will be built in our storage facility.

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

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

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

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

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

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

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

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

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

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

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

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

1 studies lend themselves to countries where you have
2 population registration and universal health care coverage.

3 So there is a natural tendency for countries like Canada,
4 U.K., and the Scandinavian countries to think of setting up
5 these studies.

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

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

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

25 What are we doing at the moment? While we are

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

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

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

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

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

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

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

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

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

1 quite high in the risk management of that.

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

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

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

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

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

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

8 Thank you very much.

9 DR. TUCKSON: Thank you very much.

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

12 DR. FITZGERALD: Yes, thank you.

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

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

19 DR. FITZGERALD: Right.

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

22 DR. FITZGERALD: Okay.

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

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

3 DR. FITZGERALD: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 This is just a schematic of the multiple levels

1 of measurement that we anticipate in the Children's Study.

2 There will be community level measures of neighborhoods,
3 schools, and communities, measures of the social
4 environment, friends, family, and organizations, a number
5 of individual factors, and how all of these interact with
6 genetics to affect health and development over the 21-year
7 time period.

8 Now turning to the recent milestones and the
9 current status of the project. After a number of meetings,
10 including deliberations of an expert panel and
11 recommendations from the Federal Advisory Committee in June
12 of 2004, the decision to utilize the National Probability
13 Sample was announced. Shortly after that, the study plan
14 was developed, and this was first presented in September of
15 2004 to the Federal Consortium. Later in November of 2004,
16 the study plan was made public as part of the request for
17 proposals for the Vanguard Centers.

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

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

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

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

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

1 the National Center for Health Statistics.

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

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

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

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

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

25 There will be no more than one award for

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

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

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

16 For the main locations, the enrollments over a
17 4-year-period in the vanguard phase, there is an extra
18 year, so it is five years. Data will be collected in both
19 face-to-face visits and remote data collections, and will
20 include questionnaires, interviews, environmental samples,
21 and observations both in the home and in the community.
22 Clinical and behavioral assessments, again, both in the
23 home and in the clinical setting, and a number of
24 biological samples.

25 This is the proposed schedule as it appeared in

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

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

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

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

25 We also want to capture both intermittent and

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

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

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

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

25 The focus was on appropriate collection and

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

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

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

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

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

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

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

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

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

25 Then we need, like everyone else, to think

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

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

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

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

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

25 There is also a great desire among patients in

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

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

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

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

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

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

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

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

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

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

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

12 We are particularly sensitive to the notion of
13 exploitation of patients. As I said, we've got a very
14 loyal group of patients. Enrollment in our studies, the
15 agreement to enroll is often in the neighborhood of 80 to
16 90 percent of patients who volunteer for studies, and
17 retention rates are often in the mid to high 90 percent.

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

25 We are working hard on collaborations. We are

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

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

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

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

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

1 are similar to other folks.

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

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

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

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

1 interesting hypotheses and questions.

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

10 If, for instance, using the model, as many do
11 when they think about these sorts of studies at Framingham,
12 if you had gone back to the original days of the Framingham
13 study and asked them to define the hypotheses which they
14 would be using the Framingham study to answer in the year
15 2005, we would have done a pretty poor job of that.

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

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

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

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

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

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

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

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

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

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

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

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

13 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 Now, I have three messages to you this morning.

11 They will reflect partly my own philosophy in what CDC is
12 doing with global collaboration with many of the people
13 you've heard from before, and I mentioned specifically a
14 couple of things.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 Now, there is also this belief that cohort

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

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

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

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

1 quality in terms of epidemiologic parameters.

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

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

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

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

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

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

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

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

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

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

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

17 The network has about 700 people right now from
18 40 different countries. It is wide open to anyone who
19 wants to join it. There is a website with information
20 exchange. There has been a lot of training and technical
21 assistance through the form of workshops that we've been
22 doing. Roughly on average, one a year.

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

1 information for policy and practice.

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

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

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

1 continues.

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

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

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

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

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

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

9 So in conclusion, these are my three messages
10 for today. One cohort study in one country is not enough.

11 There is more than one way to get there. I think all the
12 ways will get us there. What we need to do is work all
13 together to really look at this challenging area ahead of
14 us, which is how do we make sense of the Human Genome
15 Project.

16 Thank you.

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

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

1 this a very good listen.

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

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

6 DR. WILLARD: Thank you, Reed.

7 Let me add my thanks to the speakers,
8 especially for keeping to time, which will keep us on task.

9 I want to thank the members of the task force that put
10 this session together. Although she just walked out the
11 door, I want to specifically thank Amanda for her diligence
12 and hard work in getting this day scheduled.

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

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

1 regarding large population cohort studies.

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

7 Ed, I have you first.

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

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

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

24 DR. GUTTMACHER: Well, we're luckily at the
25 much earlier stage, so I don't have to claim that we

1 actually have a plan for turning it around, but we can see
2 a way that we might get there.

3 But before I even answer your question, as long
4 as I've got the microphone, let me take exception to my own
5 presentation by pointing out that since I gave the
6 presentation some many minutes ago, I have learned that due
7 to technical problems, the report that I promised would be
8 up by close of business today will still be up by close of
9 business today, but close of business today may not be
10 until the end of this week.

11 (Laughter.)

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

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

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

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

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

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

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

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

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

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

15 Kevin, I have you, and then Emily.

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

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

24 Many times in the presentations, people
25 mentioned things like the public responds well to this, or

1 we're looking for public transparency, or we have
2 altruistic participants for these projects.

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

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

20 So in this process of harmonization, what input
21 do they have? Certainly about risks and benefits, but also
22 as things go along, can they affect change? Can they guide
23 the process? Are they going to have them put into how the
24 harmonization is done? I know that's a big question, but
25 it is one that is coming up I know more and more in the

1 social science literature, and I think we need that to help
2 inform us of the best way to go forward. So I kind of
3 throw that open to anybody who might have a response.

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

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

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

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

25 I was picked up by a member of Parliament. I

1 said, slightly glibly, "We'll maintain a dialogue with the
2 participants. He said, "How are you going to maintain a
3 dialogue with 500,000 people, Dr. Newton?"

4 Of course, the answer is you can't. To some
5 extent, of course, his point was that we are the elected
6 representatives of the public. Therefore, perhaps we
7 should have a role.

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

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

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

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

1 just find ways around it.

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

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

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

18 DR. WILLARD: Thank you.

19 Emily, I have you next.

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

22 In your presentation, you were the only one who
23 mentioned that there actually was an act of Congress
24 required to fund your study. I am curious whether you
25 think that will be required for other large studies in the

1 U.S., or if this is sort of an anomaly that has to do with,
2 because it was kids, or really what the genesis of that
3 being funded by that mechanism was, and whether it is going
4 to apply more broadly to other population studies in the
5 U.S.

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

12 In terms of whether future studies are going to
13 require specific authorization, probably Dr. Guttmacher
14 could say.

15 DR. GUTTMACHER: Yes. I won't make you, Ruth,
16 responsible for funding our study.

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

24 Those would include, for instance, thinking
25 about this as a public/private partnership. Now, that's

1 not the first time that has been done. It's not even the
2 first time it has been done in genetics, obviously. But
3 the kind of funding that something like this would need, I
4 think one would need to really look at bringing in
5 non-governmental payers, the kind of data we think would
6 provide and would again be freely accessible to anyone with
7 IRB approval, which would include commercial entities that
8 had IRB approval.

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

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

24 But I think this kind of thing, if it were ever
25 to see the light of day, it would require some innovative

1 looks at funding.

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

5 DR. BRENNER: It's authorized.

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

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

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

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

15 DR. WILLARD: Barbara, I had you next.

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

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

1 DR. WILLARD: Barbara?

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

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

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

21 Then again, also around this topic of
22 recruitment. It seems that for many of these large
23 population studies, the medical institution is the place
24 where people get recruited into these types of studies. We
25 know that there are many people in the United States that

1 do not use medical institutions for their health care.
2 They don't have access to it, or they don't have insurance.

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

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

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

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

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

25 For example, I gave the example of eating beef

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

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

12 So I think it is really what we do is we use
13 proxies to define things that we really want to get at.
14 Sometimes we want to get at income. We look at it in terms
15 of African Americans, because African Americans tend to be
16 poorer than whites.

17 So it really does come down to what is it that
18 we are trying to answer? How do we design our studies in a
19 way to make sure that we have under that umbrella the
20 things that we want to measure?

21 For me, I look at ethnicity as a good way of
22 people identifying themselves. What ethnicity does, it
23 creates the flexibility for people to move between groups.

24 I'll give you an example.

25 In Nigeria, for example, where I grew up,

1 because of the way people get married and the custom, if a
2 Yoruba marries an Ebo and the woman happens to be Ebo, the
3 child is Yoruba. So the child grows up as Yoruba. If that
4 person comes to the United States and says, I'm Yoruba,
5 they have Ebo also in there.

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

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

15 That's one of the several reasons why we really
16 saw the household unit as the recruitment unit, to get away
17 from that very bias that that would obviously contribute.
18 The whole issue of race/ethnicity you'll see was one of the
19 six descriptors that we thought should be used. Ideally we
20 would think that such a study should reflect the population
21 of the United States, which means ideally it should be a
22 290 million person study.

23 That probably would be very difficult to find a
24 budget for. So what are the key things that one needs to
25 include if you're looking at genes, environment, and

1 health, and what are those other descriptors of individuals
2 that make a difference? Well, age does, gender does in our
3 society, and for similar reasons, race and ethnicity do
4 have something to do with one's health status. Now, many
5 of us suspect not much of that has to do with genetics, but
6 since this is about genes and environment, to be inclusive
7 of that, we thought we needed to include groups.

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

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

23 So if you want your study to inform about all
24 the different racial and ethnic groups, then you really
25 have no choice but to consider that in the sampling design.

1 I think that that is clear. But it goes farther than
2 that. It is insufficient just to simply say we want to
3 include this number of each of the racial and ethnic
4 groups.

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

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

18 So you have to think about exactly for each
19 group how to represent it. And then going a step further
20 than that, you have to think really hard about the
21 representation in the study. If you just go by the
22 proportionate makeup of the U.S., then it is true, it is
23 just a fact mathematically that you will have more power to
24 identify gene by environment interactions in those groups
25 that make up a larger proportion of the U.S. population.

1 You have to decide whether or not that's acceptable.

2 DR. WILLARD: Thank you for that.

3 Reed, I have you next.

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

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

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

24 DR. GUTTMACHER: We've had extensive
25 conversations, all three groups together. They are ongoing

1 consultations amongst the three of us to look at ways
2 clearly that they would interrelate. Particularly we have
3 had numerous ones with the National Children's Study
4 thinking about the ways that recruitment might be shared,
5 and the other kinds of ways that one might both for
6 logistic reasons and also for scientific ones, the ways one
7 might coordinate.

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

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

23 DR. KHOURY: My message is the same as Alan's.
24 I guess what we're doing at CDC is not to replace the AGES
25 study, but something that needs to be done anyway, whether

1 that is an AGES study or not, which is sort of this global
2 collaboration.

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

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

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

17 DR. WILLARD: Yes?

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

20 Do all of you get your funding through the same
21 appropriations committee? I mean, that may be the answer.

22 If you have different appropriations committees, then it
23 is kind of hard to control that. So all of your funding is
24 coming through the same appropriations committees?

25 DR. GUTTMACHER: Well, NICHD is part of NIH, so

1 yes, we get all of ours from the same committee. And CDC.

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

5 DR. FIHN: VA is separate.

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

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

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

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

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

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

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

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

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

22 DR. TELFAIR: Yes. I think my question had to
23 do more with the formative types of evaluation, which is
24 long term, which is looking at the process as you go. You
25 have a number of steps, a number of sort of targets along

1 the way, milestones along the way that is telling you
2 whether you are successful or not.

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

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

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

24 Those who will be looked at along the way, and
25 one would react to how it is going in terms of reshaping

1 the process as you go. It's absolutely important for
2 something of this magnitude and length.

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

5 Debra?

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

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

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

20 A final question. Is it feasible to collect
21 specimens over time? Because, Alan, you mentioned that you
22 could identify early disease biomarkers potentially, but
23 you can't unless you are collecting specimens over time.
24 So you have a specimen, rather than just at enrollment.
25 But that may not be feasible logistically from a storage

1 perspective, or from a financial perspective, but it would
2 be a shame to not even consider that as an option.

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

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

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

23 That data set would again be stored, but then
24 shared with folks who had IRB approval to use it kind of
25 thing. So very much like HapMap or something like that,

1 the data would be made freely available. Samples are
2 obviously both in terms of finances and in terms of a fixed
3 volume. It is harder to think about how to share, but that
4 doesn't mean there aren't ways to do it.

5 DR. WILLARD: John?

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

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

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

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

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

1 (Applause.)

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

6 We will get our lunch. Well, you'll do what
7 you need to do, and then you'll get your lunch. It is
8 1:20. So if you can do all of this in a hurry, and let's
9 try to sit down here at like 1:30, which is impossible, but
10 we're going to try. If I say 1:30, it will be 1:33, but
11 we'll do it.

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

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

24 See you all in 10 minutes.

25 (Recess.)

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AFTERNOON SESSION

(1:35 p.m.)

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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

1 this is not one.

2 Michael?

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

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

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

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

1 is important.

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

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

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

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

1 available?

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

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

16 DR. WILLARD: Ed, are you satisfied?

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

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

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

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

12 Suzanne?

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

19 Again, with our agency and the focus on the
20 underserved, this would be another way that investigators
21 could identify their populations. Not just urban rural,
22 but by the classification of underserved populations.

23 DR. McCABE: A different point, and that is I
24 think it was wonderful what we heard today. Like Debra,
25 I'm excited by the possibility. I think we aren't going to

1 be able to use the information from the Human Genome
2 Project without these kind of studies. So it is absolutely
3 critical.

4 On the other hand, I personally don't feel that
5 I would have at this time all the information I needed at
6 hand to say to the Secretary, you should support this
7 study, that study, or some new kind of study. So I'm not
8 sure how we can move from where we are now with this
9 wonderful introduction that we had to getting to that
10 point, but I would feel that if we were to make a
11 recommendation, we need to move beyond where we are now.
12 Or at least I would feel personally that I needed more
13 information.

14 DR. WILLARD: Kevin?

15 DR. FITZGERALD: On that note, a couple of
16 things are of concern to me, and I imagine to other people,
17 too.

18 Perhaps veiled in the global question I raised
19 earlier was a question that was trying to get at what you
20 wanted. That is, what kind of information do we think we
21 might need in order to go forward from here?

22 The idea in looking at the AGES or whatever
23 they are going to end up calling the project, when Alan
24 presented, I thought it was very interesting. In one of
25 his slides, he said public consultation should be

1 extensive. They mentioned town meetings and they mentioned
2 focus groups. I know those are two ways that are kind of
3 hot right now for engaging the public.

4 But we could even make it a more general sort
5 of question and say, if indeed as Teri mentioned, you do
6 the best that you can do, what is that? Who determines
7 what is the best we can do? Do we have that data? Have
8 they looked at those studies? Where is that information?
9 Maybe they have. Maybe that's out there. We don't
10 necessarily have it together yet.

11 Then could we, looking at that information, at
12 least suggest a process that would have a beginning where
13 again, as was mentioned, the public would have some input
14 into design? So this isn't our excitement being sort of
15 sold to the public so that they will buy in in a sort of
16 way, but to say no, they have to be empowered in this
17 entire process. Then have standards or mile posts along
18 the way to say all the way along, this is going to be a
19 potential for public interaction, review, and evaluation.

20 I imagine, as we all do, that this information
21 is going to be there, and it is going to grow and expand,
22 and it will be shared among different nations, different
23 groups, and that sort of thing.

24 So that in the end, we can say that this is
25 something that the public is definitely a part of all the

1 way along. Again, I think we're going to run into
2 questions later on, like what happens when you do find
3 something? Especially in the United States. What does
4 that mean? Is it only going to be available to some?
5 If there is a treatment, is it only for those who can
6 afford it or have the proper coverage?

7 So all those kinds of things I think need to be
8 in from the beginning. That would be the type of
9 information I think we could gather, at least at the
10 beginning.

11 DR. WILLARD: Ed?

12 DR. McCABE: There's a model, not for this
13 specific question, but for this kind of question. How do
14 you engage the public? How much information do you need?
15 How involved can they be? That's designed through focus
16 groups. That's with Kathy Hudson's Center on Reproductive
17 Genetics. The Pew Center, it's a Johns Hopkins Center.

18 So I know they have been coming out to the west
19 coast to do focus groups. From my discussions with Kathy,
20 at least, they have done a bit of a scientific approach to
21 how much information is enough.

22 DR. FITZGERALD: Just to build on that, that's
23 right. That group is one. There are a bunch of different
24 groups that are using that. Part of that comes from work
25 by Dan Yanklovich that he put together. So as I said,

1 there is material out there, and studies have been done.

2 I know that Canadians had an extensive process
3 whereby they had focus groups, task forces, and town
4 meetings to look at some of their health care issues. I
5 think we should at least start to gather that information
6 and see how we might want to build a process out of that
7 sort of thing.

8 DR. GUTTMACHER: Hunt?

9 DR. WILLARD: Cindy first.

10 MS. BERRY: I was wondering, in terms of what
11 we can recommend, if it would be appropriate for us to
12 suggest to the Secretary that when the administration
13 devises public health plans or programs, and I'm thinking
14 obesity was one that Secretary Thompson focused on, and I'm
15 sure cardiovascular disease or women's health issues,
16 whatever it is, when they launch public education, public
17 awareness, and other types of programs, that the Secretary
18 always infuse into those programs at the outset, the
19 genetic component.

20 So if maybe part of that big effort, whatever
21 it is, would involve some sort of commitment in terms of
22 funding studies like what we were talking about, enhanced
23 funding, more than what is currently being done, so that it
24 recognizes the importance of genetics in all of these
25 issues, keeps the issue out in the forefront for the

1 public, and helps to educate the public appropriately.

2 So in public education campaigns, when the
3 Secretary goes out across the country and holds the town
4 hall meetings and all these other things, genetics is
5 always there, whether it is just talking about a study,
6 encouraging people to participate in a study, whether it is
7 announcing an infusion of funds, whatever it may be, that
8 our recommendation would be that the Secretary always
9 include, or look to include where appropriate, a genetic
10 component to whatever your new public health activities
11 are. Maybe we can give a few specific examples.

12 DR. WILLARD: A point of information. The
13 Surgeon General belongs to whom in the government? In HHS?
14 Does he report up through the Secretary?

15 PARTICIPANT: Yes.

16 DR. WILLARD: Okay. Alan, you had a question?

17 DR. GUTTMACHER: And the Surgeon General is
18 actually quite aware of genetics and its role in medicine.
19 He talks about it almost every single speech he gives
20 these days. He is very much into carrying the public
21 health message of genetics.

22 I just wanted to make the point. I can hear
23 many people in the committee share, well, many of us around
24 the table have an excitement about the importance and the
25 value of these kinds of studies. Also I must admit some

1 excitement with just the intellectual aspects of how one
2 would design such a study.

3 But I should warn the committee that our
4 experience has been with this working group that it took
5 literally thousands of person hours to get this report that
6 will be up on the Web very soon, to get it that far. I
7 think the committee needs to think about how much does it
8 want to suggest specific study design issues to the
9 Secretary, or how much might it want simply to call to the
10 Secretary's attention the potential value and importance of
11 such studies and what are the design features that need to
12 be considered for such studies to be effective, useful, and
13 what are the questions about participation and community
14 consultation, involvement, et cetera, rather than going too
15 far in designing it.

16 It is going to be, I think, a challenge for the
17 committee. If you want to move in this direction at all,
18 it would be to figure how far to go with somewhat limited
19 staff time, how far you want to go down the designing path
20 versus just saying these are the features that need to be
21 taken into consideration, these are some ways to look at
22 them kinds of things.

23 DR. WILLARD: Muin?

24 DR. KHOURY: Actually, I have a couple of
25 comments for the committee, and also a comment on what

1 Cynthia just said.

2 It is very obvious at this juncture in time
3 that in order to take the Human Genome Project to the next
4 level, which is to translate it into health benefits for
5 the public's health or the population, that we need to
6 understand genes and health. That as an initiative, I
7 think this committee is very well situated to suggest to
8 the Secretary that you need to do something more than just
9 sequencing the human genome, which as HHS has spearheaded
10 with DOE and others, that we need an initiative that
11 measures the effects of genes on the population or the
12 populations.

13 That statement I think is a no-brainer, but I
14 don't want to put words in your mouth. Now, to get down
15 from there to the level of one study, two studies, or three
16 studies, you guys can decide how much more specific you
17 want to go from there. I mean, you want to enhance sort of
18 the leadership of HHS and push it a little bit, and also
19 this issue that Cynthia raised earlier about the
20 integration of genomics into everything that smacks of or
21 smells of public health.

22 You mentioned obesity. I just want to mention
23 here that this is sort of the basic principle by which our
24 little office at CDC has been operating, which is to try to
25 integrate the messages of genomics into whatever it is. We

1 have a group that's working on obesity right now. We are
2 going to be part of it.

3 We have a STEPS initiative that is department-
4 wide that involves HRSA, NIH, and CDC, which is a chronic
5 disease prevention. Of course, our Surgeon General is very
6 interested in literacy and promoting family history. So
7 there is always an angle by which we can find that trigger,
8 or the point of integration of genomics.

9 So I think these are the two points that I
10 wanted to make. One is the encouragement for HHS to sort
11 of develop agency-wide, multiple agencies coming together
12 to figure out what the genome means for health, and whether
13 it requires one study or three studies.

14 I'm not suggesting I agree with that, and I
15 don't think this committee should design one study after
16 all of the hours and many months of work that has been put
17 into the ideal design of that AGES study. But you can make
18 sort of overarching statements about the importance of
19 these kinds of studies and what HHS can do.

20 DR. WILLARD: Reed?

21 DR. TUCKSON: I think I'm sort of headed where
22 Muin is. I think the first and critical question is do we
23 as a committee know enough to believe that we should make a
24 recommendation that this is an area that should proceed?

25 It seems to me then that for me, I'm just

1 trying to write the letter in my mind, the letter to the
2 Secretary that says, Dear Secretary, we believe that we
3 need a large population study for the following reasons to
4 answer the following kinds of questions that would benefit
5 the health of the people.

6 Part of that phraseology, Muin, is what you
7 said in terms of that now that you have the genome stuff,
8 now you have to apply that. But you need to apply it and
9 understand it in ways that lead to some kinds of
10 describable deliverables, that we think it will improve the
11 health of the American people in the following ways for the
12 following reasons.

13 We believe that to achieve that, certain things
14 need to occur, like the coordination of resources across
15 the Department to determine the best use of available
16 funding and money, to determine the number of studies and
17 how they ought to interrelate so that this is efficient and
18 it makes sense.

19 I think that to me is a letter that I think we
20 could start thinking about sending. But the challenge is
21 how do you fill in now the details there?

22 DR. WILLARD: Ed?

23 DR. McCABE: The one thing I would change in
24 the opening paragraph of your letter is that I wouldn't
25 specify a study. I was convinced by what I heard this

1 morning that it is probably studies, the question is how
2 many studies, how should they be prioritized, and how
3 should they go.

4 The other thing that I heard this morning and
5 I'd like to mention that might be in the letter if the
6 committee agrees is that this might be another thing that's
7 a public/private partnership. Especially given the budget
8 where it is today, given the amount of intellectual
9 property that could potentially flow from this. We are
10 certainly already seeing that come out of deCODE Genetics
11 in Iceland.

12 I really think that this is one where, and I
13 understand the Bayh-Dole rule and all of that, but this is
14 one where I sort of feel that maybe there ought to be an
15 investment up front from the private sector.

16 DR. TUCKSON: I would just say, Ed, I agree
17 with you. I'll take it as a friendly amendment to my
18 proposal. Instead of saying "a study," I wonder whether we
19 could say "a coordinated activity." Because one of the
20 things obviously in the stage where I'm at with my question
21 was the sense, and I appreciate that Muin, Alan, and
22 everybody, that they all play together nice in the sandbox.

23 At the end of the day, you don't really get the
24 feeling, quite frankly, even though you all are talking,
25 you don't get the feeling, especially when you have

1 somebody that is authorizing language already, and somebody
2 else doesn't. You've got three multiple activities hitting
3 against the same budget activity.

4 So I'd just like to sort of see it being
5 explicitly more coordinated, whether it's one, two, or
6 three.

7 DR. WILLARD: Emily?

8 DR. WINN-DEEN: So I guess I would go even a
9 couple of steps further and say review all the existing
10 studies, analyze what the gaps are between what is already
11 going on and what we feel should go on, and then direct
12 additional funding towards funding studies or study
13 whatever is appropriate to fill those gaps.

14 I think you have to have sort of a three-phase
15 approach. The first of which is there is already good work
16 going on, right? We don't need to replicate the good work
17 that's going on. The second is where are the holes? The
18 third is then either specifically endorse a study, or just
19 more generally, which is where I would favor, at this point
20 in time since I don't think we're ready to endorse a study
21 by name at this point, to say that studies to address the
22 gaps should be funded by the U.S. government, and where
23 appropriate with public/private partnership, and just sort
24 of stop at this point.

25 DR. WILLARD: But let me push you on that point

1 a little bit. When you say "review the studies," what more
2 information would you want? In what depth? I mean, what
3 does the committee need to do to review them in order to
4 have identified those gaps beyond what we heard today?

5 DR. WINN-DEEN: I'm not sure we need more than
6 what we heard today. But it needs to be pulled together in
7 sort of a coherent single document at least. Here is the
8 state-of-the-art today, rather than a bunch of PowerPoint
9 slides, some of which we got, some of which we didn't get
10 to keep.

11 So I would like to see something that goes up.
12 Here is the state-of-the-art, here is the gap analysis,
13 and here is the recommendation going forward. The first
14 phase might be just a letter that says this is what we're
15 going to do, one, two, three.

16 DR. WILLARD: You're answering the question of
17 what the staff was going to do when they finish the
18 reimbursement report, right?

19 DR. WINN-DEEN: Well, maybe. It's a
20 suggestion. I'm not sure that our group is necessarily the
21 right one to do that evaluation. There might be another
22 more appropriate group within HHS to do that summary and
23 gap analysis. On the other hand, this might be the right
24 group. I'm not sure, because I don't know everything about
25 everything that goes on in HHS.

1 DR. WILLARD: Muin?

2 DR. KHOURY: May I be bold enough to push the
3 committee to use the word "initiative" from the Department,
4 instead of a "study?" Because an HHS-wide initiative can
5 sort of achieve the purpose of what you're trying to do
6 here, which is take the Human Genome Project and put it
7 into population hands. That is sort of the spirit of this.

8 Now, in deference to the NIH, I guess it will
9 all behoove you to wait to see that document that the group
10 has worked on tirelessly for the last few months and see
11 for yourself the amount of work that has gone into it. I
12 suspect it has a background section and everything. It is
13 not only focused on just the age of study, but it has much
14 more than that. I mean, I haven't seen it, but I suspect
15 it has all of that in it.

16 So I think as a committee, you can review that,
17 and then you can recommend to the Department an initiative
18 that takes that plus other activities that goes on within
19 the other agencies, within NIH, CDC, and develop an
20 HHS-wide initiative that could morph into one study, two
21 studies, or 15 studies. I'm not sure how it is going to
22 evolve. That study would be on the table as one of the
23 considerations for discussion.

24 DR. WILLARD: Any other points on that
25 question?

1 DR. TUCKSON: I just wanted to ask if Kevin
2 could come back, then. Kevin, if right now we have as an
3 outline here sort of that we would be thinking of sending a
4 letter to the Secretary about explaining why this was
5 important, that we would applaud the good work going on,
6 the gaps identification, the calling for some analysis that
7 leads to an HHS-wide initiative to address whatever the
8 gaps were, and then the idea of putting public money and
9 perhaps something about private money.

10 We haven't gotten to your point earlier around
11 what the American people want. Where does that fit into
12 this?

13 DR. FITZGERALD: Well, I guess it depends on
14 how you want to look at the wording that you're using. So
15 if you're talking about what are the gaps, as was
16 mentioned, we haven't seen yet what the genome website is
17 going to have on there, what the report says. I haven't
18 looked at that data yet.

19 But again, it would be another example of the
20 way in which the public can be engaged and empowered in
21 this process. That could be seen as one of the gaps that
22 needs to be addressed further. How well can that be done?
23 Is this something that is of such importance and magnitude
24 that it is going to be a significant problem? Or have we
25 pretty much found ways to address this in constructive

1 terms so we can go ahead and figure that we're going to be
2 handling these issues as they go along, because it will be
3 part of the process.

4 I would just see that as one of the gaps for
5 sure that would need to be filled in.

6 DR. WILLARD: I might raise, and I'm not sure I
7 believe in this, but I'll say it anyway just to get it out
8 here for discussion. That is I have been very impressed in
9 the U.K. by a process or a group, I think it is the Human
10 Genetics Commission or something of that sort, which was
11 representative of the public at large, which in fact
12 examined a whole host of issues that led up to the
13 formation of the Biobank.

14 They traveled around the island, met with
15 various groups of people, and collected that information.
16 It was a separate group. It wasn't led by the MRC or the
17 equivalent of any of the bodies that we have represented
18 here, because it was really the public doing its work and
19 registering its own opinions.

20 So my question of the United States is not the
21 United Kingdom, but the question is is there a need for
22 that kind of an arrangement before we would anticipate an
23 HHS-led study of half a million to a million Americans who
24 are going to have their bodily fluids sampled and stored
25 for all time, and eventually perhaps leading up to having

1 their genomes sequenced when we can do it for reasonable
2 dollars.

3 I mean, we are in a country right now where the
4 Bank of America can't even protect records from members of
5 the United States Senate. I'm not sure the public at large
6 is prepared to assume absent an opportunity to weigh in on
7 the issue, just assume that folks will get this right, and
8 that people's medical information and genome information,
9 potentially very sensitive information about medical
10 conditions that they may or may not be susceptible to, that
11 that somehow will be okay and will sit in a computer
12 somewhere.

13 So I think there may be a lot to be gained by
14 allowing the public in a very broad and far reaching manner
15 to weigh in on this issue. This is the right time to do
16 it. We did a reference sequence which wasn't specific to
17 anyone. But before we kick off a much more extensive study
18 that might involve a million Americans of many different
19 ethnic groups which will have to be represented in one way,
20 shape, or form, to allow all the representatives of those
21 groups in fact to weigh in in a clear and deliberative
22 manner. I'll throw that out to the group.

23 DR. TUCKSON: Did you convince yourself, by the
24 way, while you were talking?

25 (Laughter.)

1 DR. WILLARD: I was just getting up to steam.

2 DR. LEONARD: I agree. In listening to the
3 talks, I remember hearing the word "trust." You have to
4 have trust of the participants. My immediate thing that
5 popped into my head is can we create trust in the U.S.,
6 either of scientists, the government, or with the current
7 environment the way it is. I don't know that that's
8 feasible.

9 Maybe by doing this type of project, it would
10 at least be a step toward building trust, which at this
11 point, I think we're going to fall flat on our face.

12 DR. GUTTMACHER: Where are the data to support
13 that? I'm just curious. Because, I mean, there are
14 certainly other large studies out there that are collecting
15 genetic information in a thoughtful way that we have not
16 had in the U.S. Not to say that it's not a challenge, but
17 I'm not sure that we're entering quite so dire of a
18 situation.

19 DR. FITZGERALD: Well, I mean, just to address
20 that a little bit. I think there is some data out there,
21 and it may not be as extensive or as deep as we would like
22 it to be. There are some issues where this has been
23 addressed in a kind of different vein.

24 One has been say genetically engineered crops.
25 Part of the idea that was wrestled with there was

1 everybody is thinking, this is all great, it's wonderful,
2 it's going to benefit the public. Well, does the public
3 think it's going to benefit the public? Then you say,
4 well, they don't. Well, then that's a matter of education.

5 Once they know what we know, of course they'll agree with
6 us.

7 Well, that may or may not be the case. That
8 gets back to these other sort of town hall meetings, focus
9 groups, and that kind of thing. The whole point of that
10 process is to begin this dialogue. What I would argue too,
11 is that this is not just for this particular issue.

12 I understand, and I think pretty much if we
13 took a poll of the people around the table, we'd all be
14 convinced of the usefulness and the benefit of this
15 extending what has gone on in the Human Genome Project.
16 But I think Debra is right. We have to, as part of this
17 thing, also recommend that the government build trust.
18 This is just another stepping stone, and there will be
19 something after this, and there will be something after
20 that.

21 We have to look to the future to say what kind
22 of precedent do we want to set now so we don't have to come
23 back and revisit each and every one of these issues again
24 and reinvent the wheel.

25 DR. TUCKSON: We've got five minutes to resolve

1 this.

2 DR. WILLARD: I've got Robinsue first, and then
3 Muin.

4 DR. FROHBOESE: Thanks. As the representative
5 from the Office for Civil Rights and the office within the
6 Department responsible for the HIPAA privacy rule, I just
7 wanted to remind people of the rule, and the fact that we
8 are working with the public in general to really raise the
9 consciousness level of consumers and their rights to
10 privacy of their health information.

11 But we also have been actively working both
12 with CDC and NIH, and have issued guidance with both NIH
13 and CDC on research, both from the public health
14 perspective, and more general research issues. Research
15 specifically as it relates to the privacy rule and
16 protecting privacy interests.

17 DR. WILLARD: Muin?

18 DR. KHOURY: As a follow-up on your comment
19 earlier, Hunt, about the British way of how they went about
20 it with the Generics Commission. I wish John Newton was
21 here to explain more.

22 But if there is such a group in the U.S., I
23 maintain to you that this committee comes as close to that,
24 I mean, the name Genetics Health and Society implies that.
25 You are advising HHS.

1 If you want to undertake sort of the martialing
2 of the post-genomics or the genomics era and how to
3 translate the genome into health benefits to help society.

4 I mean, your group, if you decide you want to undertake
5 such a process to help the Department undertake such an
6 initiative, would be the right thing. That's up to you.

7 DR. TUCKSON: We need specific recommendations
8 as to how to proceed. You've got four minutes.

9 DR. WILLARD: I can't read your name, so I'll
10 call on you.

11 DR. FOX: I'm Ellen Fox.

12 DR. WILLARD: You're not Willie May, even
13 though you're past the sign.

14 DR. FOX: Reed, in your suggestion regarding
15 the wording of the letter, you mentioned looking at gaps,
16 and then looking at where there were gaps, assuming the
17 government would fill them. Perhaps in association with
18 public/private partnerships.

19 I think there needs to be a little more
20 attention, and there hasn't been much discussion today, but
21 somehow I think we need to address the issue of the
22 appropriate role of the government relative to the private
23 sector.

24 I wouldn't want there to be an assumption that
25 the government should just fill all the gaps that exist in

1 this endeavor, particularly when there is an opportunity
2 for private industry.

3 Also when we were talking about public/private
4 partnerships, I think we need to be very careful about
5 that. I think that in the U.K., my understanding is there
6 were some concerns among the public about the
7 commercialization aspects. That was a particularly
8 sensitive issue.

9 In our own experience in VA, this was I think
10 the single most controversial aspect which caused us to
11 actually completely reverse our course and pull back from
12 our original thinking on the issue, because of significant
13 concerns raised about the relationship between public and
14 private sectors.

15 So I for one would like to see some language in
16 this letter that acknowledges that tension.

17 DR. WILLARD: I have Joe first, then Alan, then
18 Kevin until we get cut off by the Chairman.

19 DR. TELFAIR: I'll pass on my comment. I'll
20 wait. That's okay. I'll pass on my comment.

21 DR. GUTTMACHER: And I'll try to speak very
22 quickly. I think, again, I agree with Muin's point that
23 this group is as close as we have to the U.K. Commission.

24 It seems to me that it gets back to this
25 question of how far you want to go down the road of

1 designing the study. What would make most sense to me
2 would be simply strong wording the letter to the Secretary
3 that it is just completely vital to the success of any such
4 study that community participation be often, early,
5 frequent, ongoing, and giving ideas of the kinds of ways
6 that might be achieved, rather than going out and doing
7 that first.

8 We know that it is necessary, so just make it
9 very clear that that really needs to be done, it needs to
10 be meaningful, and it needs to use the latest state-of-the-
11 art kinds of things to do it, and maybe invent some new
12 ones.

13 DR. TUCKSON: I think we've got a good sense of
14 a charge to our committee. We have a good committee that
15 put together one heck of a discussion today. Clearly they
16 are focused and know what they're doing.

17 I think the overall committee has given pretty
18 good specificity as to first of all, there is a consensus
19 that I hear that's very strong that we do want to
20 communicate with the Secretary about this. I see a very
21 strong consensus that we think that this is an important
22 area that needs to go forward.

23 I think that we have agreed at least to charge
24 our subcommittee with the task of fleshing out the first
25 draft of a letter that would say why we think this is

1 important in terms of the health of the people. Why it is
2 important, as Muin's language was, that says that having
3 done the human genome, putting it into play is for the
4 benefit of the health of the people. This is an important
5 thing to do. So I think that's important.

6 Secondly, we do want in this letter to praise
7 the good work that is already going on. Third, we're
8 calling for some type of a gaps identification. We are
9 then calling for a coordinated effort which we are using
10 the suggested word "initiative" as opposed to a study that
11 would address the gaps.

12 We are clearly saying that one of those gaps is
13 looking at what is important to the American people, and
14 seeing what we need to say there. We are saying that we
15 would be calling for public money, but also perhaps, and
16 this is something for you to look at in a little more
17 detail, private dollars.

18 We just heard a comment around maybe even
19 putting in something that has to do with the appropriate
20 relationship between the public and private sector on
21 initiatives such as this.

22 Then finally, what we didn't resolve, but I
23 think we have given a mandate for you to look at is this
24 notion then of the question of establishing trust, which I
25 think is related to the gaps around what American people

1 want, and how that might be phrased.

2 I don't think we were as prescriptive as the
3 rest of the letter, but we leave it to you to take the
4 sense of it.

5 Kevin, I'm not sure whether you're on that
6 committee. You are on it?

7 DR. FITZGERALD: I'm not on it.

8 DR. TUCKSON: But I would urge you to connect
9 to the committee and get your points in.

10 With that, I think we have the expectation,
11 Hunt, that as the Chairman of that subcommittee, that we
12 will get a report back from you with a draft before the
13 next meeting. Our commendations for an excellent set of
14 presentations today.

15 All right. We're going to move to something
16 which, again, we need to be very disciplined on our
17 discussion of this billing and reimbursement. You have a
18 page in front of you.

19 Does everybody have it? I'm going to just take
20 you through really quickly just the logic of this. Then
21 when we discuss it, we need you to be focused in on the
22 logic and on where you are on the page. We can't have
23 people going all over the universe today on this. We've
24 got to bring this to closure.

25 Number one. What this paper says is let's get

1 on the table or off the table. The question of whether or
2 not today genetic counselors who are certified ought to be
3 able to bill independently, because they in fact have a
4 certification that would thereby make that possible.

5 So the language sort of says right now, do we
6 believe that there is sufficient reason, is there a reason
7 overcoming the barriers that we identified in this report,
8 is there a reason to warrant, and are there sufficient
9 evidence, criteria, and processes that would support a
10 recommendation that non-physician health professionals who
11 provide genetic counseling services that are deemed
12 qualified should be able to bill directly for their
13 services.

14 Would this apply to all payers? Or only public
15 insurance? Such a recommendation then would in fact allow
16 these health professionals to independently practice
17 genetic counseling. That's first.

18 If we said that that were true, if we believe
19 that that is a recommendation that we would want to make,
20 then the question would be how you would implement
21 something like that. Would you take as a strategy that
22 licensure where available, then be able to use it because
23 they had licensure in a certain state?

24 In those states where it was not available,
25 that because you were recognized by the ABGC, or the GNCC,

1 that that would be sufficient to allow that to occur. Or
2 that you'd leave out the licensure part altogether and just
3 simply say, let's just make it the certification. Or that
4 the Secretary would use his leadership to influence the
5 establishment of a single body that would oversee the
6 certification of providing these genetic counseling,
7 similar to the role played by the ABMS for physicians that
8 would have the functions as listed there.

9 This "or" after that should not be there. It
10 should simply be that this needs to be done expeditiously
11 if it were to occur. So again, it would be that the train
12 would start to leave the station, and while it is leaving,
13 the Secretary would be asked to use his influence to help
14 facilitate the creation of this body that would continue to
15 study it, even while the event was already begun.

16 If you believe that there is not sufficient
17 evidence to do this today, that we're not going to make
18 this recommendation and we can't make that recommendation,
19 would we then say okay, we've got to urge the creation of a
20 body to answer the questions that we are unsure about, and
21 that that needs to be done expeditiously with perhaps some
22 hope for time scale to determine the answers to things like
23 which providers are qualified under what conditions, under
24 what supervision, and how they should be reimbursed.

25 This analysis should also assess the

1 effectiveness and value of genetic counseling as delivered
2 by various health providers in different settings, assess
3 how barriers to billing and reimbursement are affecting
4 patient access, and so forth. So those would be the things
5 that would be called for urgently and quickly to get done.

6 Then in the interim, while those things are
7 happening, whatever it is that is going on, because it will
8 take time, either one, Option A or B, there are certain
9 things that we worked hard on yesterday to agree on.

10 That was in the interim, the Secretary should
11 direct government programs to reimburse prolonged service
12 codes, HHS with input from the various providers of genetic
13 counseling service should assess the adequacy of CPT and
14 E&M codes, non-physician providers who are currently
15 permitted to bill directly under any health plan should be
16 eligible for an NPI, and then finally, that for those who
17 are billing incident to a physician should be able to
18 utilize the full range of CPT and E&M codes. So that's the
19 logic, that's the flow of it.

20 So the first thing to get on or off the table
21 is what do you believe about the need and/or, relatedly,
22 the ability to make the determination right now that
23 genetic counselors who are in some ways certified should be
24 able to counsel independently and bill independently? What
25 is your thought about that? Put it on the table, or take

1 it off the table? The floor is open.

2 And Debra Leonard is not here. Let me just get
3 her point in right away. Debra has been emphatic to the
4 point of she jabbed me in the chest when she was talking,
5 make no mistake that she believes that the answer is yes,
6 that they should be able to. I'll get to what her strategy
7 for implementing that is. But she is one person that says
8 it should be done now.

9 Barbara?

10 MS. HARRISON: And I as well say an emphatic
11 yes. Under yes, I think that we should say the first
12 statement wherein states licensure is available, skip the
13 second one and go to the third one where the Secretary
14 would use his leadership. Also --

15 DR. TUCKSON: That's all. You only get on that
16 one.

17 MS. HARRISON: Just for clarification.

18 DR. TUCKSON: Okay.

19 MS. HARRISON: The "in" in the interim part is
20 going to be there regardless? Is that what you were
21 saying?

22 DR. TUCKSON: Yes.

23 MS. HARRISON: Okay.

24 DR. TUCKSON: Yes, that's already there. Okay.

25 DR. FRIES: I also fully agree that there is

1 sufficient reason to recommend that they be able to do
2 this. I think that genetic counselors and certified nurses
3 have established a training program and an evaluation
4 process.

5 I think it is very clear. I think we also had
6 adequate demonstration of that before. I think that if you
7 look at the proof of practice, it is already demonstrated.

8 So I emphatically believe that yes is the answer for this.

9 I would recommend that the third comment there, "Secretary
10 using his leadership and influence to establish a body of
11 certification," I think that would move towards assisting
12 this group in obtaining licensure.

13 Once they had licensure, this would be a
14 no-brainer. It would already be established.

15 DR. TUCKSON: Okay. Other comments, please?

16 Yes, sir?

17 DR. ROLLINS: I think that licensure and
18 certification is not sufficient to make a recommendation
19 that non-physicians be able to bill directly for services.

20 From our discussion yesterday, as I said, if
21 we're going to be using evidence-based medicine as a basis
22 for making recommendations, they did not provide evidence
23 that non-physicians were able to effectively make those
24 type of determinations compared to other groups.

25 There were not enough studies from an

1 evidence-based perspective which would justify my opinion.

2 DR. TUCKSON: So we've got three that are
3 saying yes, and one so far saying no.

4 MS. BERRY: I would say yes with the caveat
5 that when we were talking about Medicare and I deferred to
6 James and others, we can't, and the Secretary can't just
7 declare, we are going to now allow these folks to directly
8 bill Medicare. I believe it would require some sort of
9 change in the statute.

10 Correct me if I'm wrong. If that's the case,
11 then our recommendation should be more towards urging the
12 Secretary to work with Congress on legislation that would
13 do that. In doing so, it would be incumbent upon the
14 different groups to convince the sponsors in Congress and
15 to convince the Secretary to provide the evidence that
16 James is talking about.

17 DR. TUCKSON: Okay. So James, you have to take
18 away your philosophical hat. We are not at a technical
19 question purely in terms of if we were to make such a
20 recommendation, now we are talking about the language.

21 So can the Secretary cause this to occur, or
22 does it have to be a Congressional change?

23 DR. ROLLINS: I think it would require a
24 Congressional change. But also, I would say that if there
25 were some type of demonstration through the use of some

1 types of studies which show that they were as effective --

2 DR. TUCKSON: Different issue.

3 DR. ROLLINS: Okay.

4 DR. TUCKSON: Okay. So the answer is that for
5 those who are saying yes, that this should happen, the
6 technical way in which a yes gets transmitted to the
7 Secretary is that we recognize that he or she may not have
8 the power to by the stroke of a pen, cause it to occur, but
9 it has to work through the Congress. That would be the
10 language. So that's just a technical issue.

11 MS. BERRY: Just for Medicare. Now, the
12 private sector, that's a different thing.

13 DR. TUCKSON: Right.

14 MS. BERRY: We can make all sorts of
15 recommendations that is harder for the Secretary to
16 influence.

17 DR. TUCKSON: All right. So we're at four to
18 one.

19 DR. FITZGERALD: I would also like to say yes.

20 Maybe take into consideration the fact that when we talk
21 about evidence-based medicine, we always have to look at
22 who were the people who set the standards for what counts
23 as evidence? How do we go about getting that evidence?
24 What sorts of motivations have there been in the past to
25 get that evidence?

1 If this profession is seen in its proper role
2 as a profession to be reimbursed, then of course that will
3 also help I think instigate more research into how it can
4 be done better, which of course will be based on studies
5 that will look at the evidence. I'm sure the evidence will
6 confirm what we're saying, but it will also lead to the
7 sorts of improvements and the sorts of gathering of data
8 that we're talking about that would also be a good thing.

9 So in one sense, there is a bit of a Catch 22
10 here in the sense that there hasn't been the motivation,
11 and there hasn't been the emphasis in the past to gather
12 the evidence in such a way as to answer those specific
13 questions. I think people's experience can also be seen as
14 evidence.

15 DR. TUCKSON: We're at five. By the way, I did
16 a disservice to the conversation by not making one
17 statement up front. Let me rush to make it. It is this.

18 We had a lot of discussion yesterday about this
19 issue that got to the nature of respect for these
20 professionals. I have talked with almost everybody on this
21 committee at some length about these issues. The one thing
22 I want to take off the table for this discussion is that
23 there is not a single person around this table who has
24 anything but respect for the professionals who are working
25 so hard to do this kind of counseling.

1 Those who may feel differently about this issue
2 do not come at it because they don't care or respect their
3 colleagues in this field. I want to just make sure that
4 that is on the record.

5 I think it is a very important point, because
6 otherwise, it could have the effect of chilling the
7 discourse. If you are viewed as whether or not you are up
8 or down on genetic counselors, you get beat up when you
9 walk to McDonald's.

10 I don't want that to be on the table. That is
11 not appropriate to do that to anybody on this committee.
12 Let's move around and see if there is anybody else.

13 DR. TELFAIR: Thanks, Reed.

14 You saved me from having to say that. That was
15 going to be my comment, because I'm voting no on this. I'm
16 voting no because I do think that it will be a stronger
17 case if you take the effort of building the evidence.

18 Clearly what is in place right now, from my
19 understanding from yesterday, and if I heard it wrong, I
20 apologize. It is still in the early stages. Everything is
21 in the early stages. Even those who have received this
22 level of verification are only two or three years out. So
23 there really hasn't been enough time to build that
24 evidence.

25 It seems to me that we need to really push

1 doing that a little bit more. So that's where I'm coming
2 from. I am one of the ones that really pushed to
3 expeditiously get it done. I think it can be.

4 DR. TUCKSON: Agnes, Hunt, and then we'll go
5 around.

6 MS. MASNY: I would say yes, that we should go
7 for the first proposal. The one thing I think that when
8 the committee presented yesterday is that I don't think
9 that they were asked to actually present all the evidence
10 base about what we're discussing now that the genetic
11 counselors or people that are providing these kinds of
12 services actually do provide efficient, cost-effective, or
13 whatever it was.

14 I think that maybe if in fact we wanted that,
15 that we could ask that specifically for this committee.
16 But I don't think that would be necessary. I think that
17 maybe if it had to go to Congress, that that information
18 could be presented from the group itself to go along with
19 that recommendation to Congress.

20 I would though say that I would rather have
21 that without reference to licensure, because I think
22 licensure is affected mostly by states. I don't, again,
23 from the Secretary's perspective, know whether he has
24 jurisdiction over state effects, certification by AGCC,
25 GNCC, and other certifying organizations, since there are

1 other certifying organizations.

2 DR. TUCKSON: But for right now then, you are
3 on the yes side?

4 MS. MASNY: Yes.

5 DR. TUCKSON: Hunt?

6 DR. WILLARD: Just a point of clarification and
7 correction for Joe. The profession of genetic counseling
8 has been around for 20 years.

9 DR. TELFAIR: That was not my point. That was
10 not what I was saying.

11 DR. WILLARD: But it was interpreted that way
12 by some. Good.

13 I'm still where I was yesterday. I'm persuaded
14 by the statement, particularly from James, that there is
15 just not a base of evidence sitting in the literature that
16 tells us yet, those of us who have done this on the front
17 lines, that this is in fact a critically important field
18 that is making a valuable contribution, and a contribution
19 that is absolutely in the middle of the road in terms of
20 how to bring genetic information to the public at large.

21 So I recognize that there is a gap, that the
22 profession of genetic counseling is likely to be critical
23 to filling that gap, and yet I don't see in the medical
24 literature the data that would be necessary to make the
25 case to the Secretary that in fact the drastic changes that

1 I think are needed will be needed soon.

2 So I'd have to vote no, but would then urge
3 that we change some of the language to be much more
4 forceful about the expected role that we see for the
5 profession of genetic counseling as we go forward.

6 DR. TUCKSON: Okay. We'll come back to that,
7 then. All right. I missed a hand here.

8 DR. FRIES: Yes. I just wanted to point out
9 that while evidence-based medicine is a wonderful tool for
10 all of us to evaluate our practices by, unfortunately
11 evidence-based medicine does not apply to every medical
12 practice that we do and that we reimburse for.

13 For example, there is not a lot of large
14 randomized, blinded, control trials just about anything in
15 genetics. So if we use that to drive our old policies, I
16 think we are being premature in this. Much of medicine
17 does not have that basis. That doesn't mean that it is not
18 justifiably reimbursed.

19 DR. TUCKSON: Good. All right. Here is what
20 we're going to do. I'm sorry. A comment?

21 DR. ROLLINS: I was just going to make a
22 response to that. It is true that a lot of activities that
23 we do in medicine, there have never been randomized
24 clinical trials to show that they work. But that doesn't
25 mean that observational studies were not performed.

1 You might even have to resort to such things as
2 a cross-sectional study to use as an evidence base. But it
3 is sort of like what David Eddy has said. Seventy percent
4 of the things that we do in medicine have never been tested
5 to see whether or not they work. We just do them because
6 we think they work. Because of that, we tend to justify
7 what we continue to do.

8 DR. TUCKSON: All right. This has been a very
9 good discourse. Very rarely do we actually take votes on
10 stuff, but right now I need to just sort of take a vote of
11 the committee.

12 I wanted to have the ex officios who weighed
13 in, I counted your votes, because first of all, you're
14 valuable here, and it is important to hear you. You had a
15 lot to say about this.

16 I want to see right now for the committee
17 members that are here. Wait a minute. There are seven?
18 Now, we had Debra. She clearly left. So does she count in
19 the seven? I think she was pretty clear. There was no
20 question about it.

21 MS. CARR: She makes eight.

22 DR. TUCKSON: She makes eight? All right. Of
23 the eight committee members that are here, those members
24 who are here who are voting yes, would you raise your
25 hands?

1 (Show of hands.)

2 DR. TUCKSON: So we've got one, two, three,
3 four. Okay. And those that are voting no, what do we
4 have?

5 (Show of hands.)

6 DR. TUCKSON: One, two. So four to two. I'm
7 trying hard to be diplomatic.

8 DR. FITZGERALD: I'm not a voting member yet.
9 I haven't passed through the hoop of fire.

10 DR. TUCKSON: You actually would have tipped it
11 more towards the five to two than the four to two, if I
12 understand you correctly. So that's what that is, which is
13 an important sense of the committee. So I think the
14 committee has got a sense of it. That's where we are on
15 the issue.

16 Now the question becomes how do we phrase the
17 recommendation about how this would go forward? So now,
18 let's specifically focus in on, and I'd like to put as the
19 first way of focusing in on this would be, I'm looking for
20 the greatest agreement possible.

21 I'm wondering whether that is around the
22 language of the Secretary using leadership to expeditiously
23 cause something to happen. I'm just trying that first to
24 see where that takes me. Now everybody has got to get on
25 board. We decided that we're going to make a

1 recommendation.

2 Now the question is how do you make that
3 recommendation work? Who has got a thought there now about
4 which of these options is the best way to make this
5 recommendation happen? What is the most responsible way of
6 getting this done?

7 DR. TELFAIR: Reed, a point of clarification
8 before we get started.

9 DR. TUCKSON: Please.

10 DR. TELFAIR: Does the vote for yes negate the
11 need to gather information independent of how it is done?
12 There are varying ways. I agree with James that there is
13 more than one way to gather information. I am just
14 wondering whether those who voted yes, because that is not
15 on the list.

16 DR. TUCKSON: The answer is that what I was
17 trying to do by making that sort of point of departure now
18 by saying the Secretary gets involved, and that all those
19 sort of gathering the information things are the things
20 that we urge the Secretary to cause to happen, is a way of
21 trying to close the gap between the yes's and the no's.

22 Now, you can decide of course to do it a
23 different way, but I was being fairly transparent, or
24 trying to get everybody at least on a common next step.
25 But it may not work. So please, who has a suggestion about

1 how now based on the things that are on the page and/or
2 something new, about how do you achieve this.

3 It has got to be a specific recommendation, it
4 has got to take us from Point A to Point B. We can't talk
5 about the theory of it anymore.

6 DR. FRIES: I was going to ask Barbara
7 specifically as a genetic counselor herself, what area does
8 she feel would specifically benefit the field the most.

9 MS. HARRISON: I think a general recognition of
10 genetic counseling as a legitimate field, legitimate
11 service, is really what would be most helpful. I think
12 everything after that will fall into place.

13 DR. TUCKSON: So you got that. That is already
14 done by the vote. So now what do you do? How do you
15 implement it? So let's be specific.

16 Do you say that everybody who is right now an
17 certified ABGC or GNCC would be someone that we would urge
18 the Secretary to, and go back to the language that Cindy
19 said again, the Secretary for the government has got to
20 urge Congress to say that if you have those degrees, those
21 certifications, you should be able to go right in and do it
22 now? Or do you say that you want the Secretary to cause
23 the right people to be pulled together to give the best
24 advice as quickly as possible to answer these questions
25 about how to do it, and then take that to the Congress? Do

1 you take it as one step, or two steps?

2 MS. ZELLMER: Maybe I'm totally
3 misunderstanding. I think the things on back about direct
4 billing for prolonged services in the CPT codes, I think
5 all are very important. All of the things on the front, to
6 me, I'm not really sure. I think they affect licensure,
7 which I don't think we would have any role over, or
8 certification, which again, I don't know that it's that
9 important that we have some kind of national certification.

10 Maybe I didn't get the point of yesterday. But
11 I think that do we need to even go here? I mean, I agree
12 with all of the recommendations on the back, but are any of
13 these recommendations under yes, something we really want
14 to do?

15 MS. HARRISON: I think the issue of licensure
16 and certification, I agree, may not be an issue that we
17 specifically have purview over. However, the main impetus
18 behind us even getting into this is an access issue. It is
19 an access issue, and it is a quality of care issue.

20 That's where I think the licensure and
21 certification comes under. So we're trying to make sure
22 that the people who bill for genetic counseling services
23 are qualified to do so, and I think we agree as a committee
24 that genetic counselors are qualified to do that, that
25 nurses are trained are qualified to do that.

1 That is where I think the licensure and
2 certification comes in. Mentioning licensure here is no
3 more saying that the Secretary has purview over that no
4 more than me mentioning certification here. I don't see
5 why it has to be either licensure or certification.

6 DR. TUCKSON: Kimberly, the issue really just
7 became one of, and you are raising an important option. It
8 is to stay moot about it. The question is how do you make
9 sense out of who is in fact a legitimately qualified
10 person. Right now, there does not seem to be any real
11 organization that allows you to figure that out.

12 MS. ZELLMER: I'm not convinced that 95 percent
13 of the physicians who give advice on genetics are
14 qualified. I don't really see this as an access issue. I
15 think that it is important that you get information from
16 qualified professionals, but I think that that issue is a
17 totally different issue.

18 I think it deals with the broader medical
19 profession in general. I don't think that we should limit
20 it to say we've got to get qualified genetic counselors.
21 I think we've got to get medical professionals who have a
22 basic knowledge of genetics.

23 DR. TUCKSON: Good point.

24 Next?

25 DR. FITZGERALD: As far as the certification, I

1 mean, one way since you're talking about it, could there be
2 multiple steps to this. We have certification processes,
3 and the training and everything like that. Could you start
4 by saying here is the starting point. Genetic counselors
5 and nurses who have gone through the certification program
6 are going to be accepted as certified. Now you need some
7 group to come and look and see if, as Joe was mentioning
8 yesterday, are there others that would be included under
9 that umbrella?

10 I mean, I think you've got a starting point
11 with the ABGC and the GNCC. Then you can see from there
12 where you might want to go.

13 DR. TUCKSON: All right. This is a very
14 specific recommendation. That's a very specific step. So
15 if we understand it here, it is the idea.

16 Kimberly, I'm trying to figure out what to do.
17 But again, at the end of the day, there is a sense by many
18 people, there is a need to try to understand. If somebody
19 is going to say, I am a qualified person and I therefore
20 should be able to bill for this service, and I should be
21 able to do this service and get reimbursed, any reasonable
22 paying organization is going to say well, who are you?
23 Under what criteria are you saying that you are in fact
24 legitimate and able to do it?

25 You're right, Kimberly. Your point is that

1 you've got doctors and others who may not, but we're
2 looking at this issue here. So the notion is that what we
3 have as a specific suggestion is that you take the
4 certifying bodies that exist today, and you say okay, this
5 is a good starting point. Then you urge the Secretary, if
6 I understand you, to create, or to try to use his influence
7 to try to create or stimulate the formation of a body that
8 would then deal with all the one offs that are going to
9 come up, the single gene people, somebody without a Masters
10 degree, who know who decides. I'm in the club, put me in
11 the club. So somebody has got to figure that out.

12 You are asking for two things at once. Start
13 one place, and then create an environment that figures out
14 how to do it with all the people that are not in this group
15 right now. That's a suggestion. So you've got something
16 to shoot at. Now, let's decide. Is that the way to do it
17 or not?

18 DR. TELFAIR: Can I just make a friendly
19 amendment to this? I think it's important to take this
20 suggestion if we're going to take it, and it be very clear
21 about the nature of it.

22 There is a siloing of risk here. You need to
23 eliminate that. If you're going to get groups to work
24 together, it needs to be on common ground. So if we're
25 directing or making a strong suggestion, then we need to

1 make sure that the group, whatever is formed, is a group
2 that works towards the common ground in a collaborative way
3 to make this happen. I just want to add that language.

4 DR. TUCKSON: That's a very important point.
5 And by the way, I want to make the moderating comment that
6 Cindy's point is I think very, very important in a
7 realistic way.

8 This is going to be subject to a public
9 discourse beyond our recommendation. So that I think what
10 we're doing is we're signaling a direction. We are also
11 signaling caveats that need to be carefully considered in
12 the interim period while this goes through the public
13 policy discourse.

14 Again, the Secretary cannot just with the
15 stroke of a pen make any of this happen. So we are
16 signaling things that ought to occur, and hopefully
17 stimulating a lot of people in this room, and those that
18 are on the webcast who are listening to this carefully, to
19 create the details that are needed. So we're fast
20 forwarding this whole field simply by the recommendations
21 that we're making.

22 That is what I think is ultimately occurring in
23 this room right now. Somebody's hand I missed. All right.

24 Specifically, is Kevin's point the one that wins or not?
25 Somebody has got to knock it down, because right now it is

1 gaining momentum.

2 DR. FEETHAM: I would just remind everybody of
3 Barbara's comment. I mean, to me the three messages are
4 the need for genetic counseling services, and we have been
5 consistent on that language, by qualified providers who are
6 of many disciplines.

7 The point of access, I mean, this bottom line,
8 again, for the good of the American public, what are we
9 talking about? Those are messages. By the way, to do
10 this, we need reimbursement.

11 DR. TUCKSON: All right. Kevin has got it on a
12 going, going, gone basis.

13 Agnes?

14 MS. MASNY: Well, I think that if we went with
15 Kevin's recommendation, what would happen is that that
16 would actually limit the number of health care providers
17 that people would have access to. I think we want to make
18 sure that people do have the access.

19 The main point that I think we're trying to
20 continually get at is that the public needs access to
21 qualified health care professionals, and that genetic
22 counselors are qualified. They should have access to
23 reimbursement.

24 DR. TUCKSON: Now, I'm not sure though, and I
25 want to respect your point, even in rushing this thing

1 through. But I'm not sure that I see the limitation.

2 I think what Kevin is saying is you've got a
3 place. You are signaling that we accept that there are
4 some people who have created something that makes sense.
5 Then he is saying expeditiously let's get to the process of
6 how do you create the requirements, the conditions, and the
7 processes that allow others to be designated. I don't see
8 how that is diminutive.

9 MS. MASNY: Not diminutive, but in terms of
10 limitations that we are now going to create another sort of
11 more centralized body for certification.

12 DR. TUCKSON: Right. Now, the philosophy here,
13 just to make sure that everybody is clear on this, is that
14 you could then, the alternative, and I don't know whether
15 this is what you have in mind. The alternative would seem
16 to be that every organization with an interest in this
17 could then certify, designate, and say okay, well, me, too.

18 So at some point, you are sort of left with if
19 you are trying to pay for this, or you have to administer
20 this or make use of this, or worry about a malpractice of
21 this, it is like well, who are you? I mean, somebody
22 somewhere along the line, and I think what he is saying is
23 he has to make sense out of this so you don't have the
24 wild, wild, west. I certainly don't want them coming to
25 us.

1 DR. FRIES: It appears to me that there is some
2 sort of a parallel for this in thinking about it in the
3 capacity of certain physician skills. For example, if I am
4 someone who wants to just simply do spinal surgery, I must
5 first of all qualify as an orthopedist, and then perhaps do
6 a subspecialty in spinal work, and then I only get to work
7 on the sacrum.

8 I have made that my derivative. The same way
9 for someone who is a single-disease counselor. That person
10 must first of all qualify in the general capacity before
11 they can then focus. So the point I'm trying to make is
12 that there is an existent certification process for someone
13 in general. If someone chooses to be in a very minor part
14 of that practice, they must first achieve that, and that's
15 already in place.

16 DR. TUCKSON: So what I think you're saying,
17 for the purposes of this activity, is A, we are not
18 trained, smart enough, or have the time to figure all that
19 out. B, we know that somebody needs to figure it out, and
20 we are urging the Secretary, therefore, to figure it out,
21 or to use his influence to convene those that are necessary
22 to figure this out.

23 DR. FRIES: That's sort of an overview of what
24 I was commenting on. But the point that I'm saying is that
25 there already exists sufficient certifications in place.

1 DR. TUCKSON: So those are models that might be
2 used to apply to this activity. Or are you saying push
3 this into existing forums that are already created to do
4 this kind of work?

5 DR. FRIES: Certification in some field. For
6 example, to become an OB/GYN doctor, I go through a board
7 examined to certify. That's already set in place. Same
8 process for genetic counseling.

9 Licensing, as we all know, is a state process.
10 The reason I raised my question to Barbara was not that I
11 think the Secretary has to do this, but whether that would
12 be politically the most advantageous thing to the genetic
13 counselors, or whoever is going to do it, to help them move
14 forward.

15 DR. TUCKSON: All right. I saw one other hand.
16 I want to do that. I missed you.

17 In fact, it was you, Kimberly.

18 MS. ZELLMER: The only question I had is
19 whether this is really what the genetic counselors want. I
20 think if they would like us to give the message to the
21 Secretary that we need some national certification to make
22 sure that people are qualified who are giving genetic
23 counseling services, I'd be much more supportive of it.

24 But I guess I just would want to make sure that
25 that is what they are interested in.

1 DR. TUCKSON: I guess the challenge we have
2 there, and Kimberly, I appreciate that. We did hear
3 wonderfully from the genetic counselors yesterday. They
4 gave us good input. At some point I think the committee
5 has to decide what it thinks it wants to do. We got a lot
6 of input. We have differences of opinion even around our
7 own table. So I appreciate the point.

8 The genetic counselors were able to express, if
9 I can try to summarize what we heard, that they have their
10 mechanism. There were a couple of organizations that spoke
11 eloquently about what they do. Even in their own
12 discourse, there were some issues that came up as to
13 whether or not you only have Masters level nurses. They
14 have their own challenges that they have to work through
15 together.

16 What they did not do, and were not asked
17 fairly, according to Agnes' point, they were not asked to,
18 but they did not teach us about what to do with the single
19 gene people and all the other permutations of issues. So
20 we don't know quite what their guidance is on that point.

21 To conclude this. I'm trying to do a quantum
22 calculus here to get your point in here. I can't figure
23 out a way to do it, other than to simply say that I don't
24 think that we can be more prescriptive than what we have
25 gotten to.

1 I don't know whether it should be that this all
2 goes and just gets pushed into the ABMS, which it can't, or
3 something like that. At the end of the day, we can only do
4 the best that we can in terms of this recommendation, and
5 then let the process unfold as it needs to. We are making
6 a pretty clear statement.

7 This is a bold statement, I think, to make,
8 quite frankly, in terms of moving this field forward. One
9 that is of concern to a couple of our members. So I think
10 we have pushed this pretty far. I think what the next step
11 is, and again, by the way, the other issue here is that the
12 reimbursement committee report is going to go out for
13 public comment, so we're going to get a whole lot of stuff
14 back anyway. This is not the last time we're going to see
15 this. We are probably going to get beat up on all sides.
16 Then we'll have done our job wonderfully.

17 Cynthia?

18 MS. BERRY: Can I just make a recommendation
19 that sort of builds on what Kevin had articulated? That
20 is, following the model of registered dieticians, the way
21 they got some coverage under Medicare for medical nutrition
22 therapy for certain cases, I can't remember now whether it
23 was diabetes or cardiovascular disease, but anyway,
24 something like that, there were a couple of indications was
25 that Congress put into the statute that the National

1 Academy of Sciences would conduct a study and look into
2 many of the same issues that we have at the top of the back
3 of this paper here dealing with cost-effectiveness,
4 appropriateness, and all of that.

5 Then based on that study, and it was done,
6 Congress looked at it and said, oh, for these two
7 indications, it does make sense for these individuals to be
8 able to directly bill Medicare for their services.
9 Therefore, we will allow that to happen in those cases.

10 So what if our recommendation is asking the
11 Secretary to direct NAS, or to fund some study mirroring,
12 using the registered dietician model. That would be a next
13 step closer. It would obviate the need really for Congress
14 to step in initially and actually authorize the study. I
15 mean, the Secretary theoretically could direct some funds
16 that way, but it may ultimately be that Congress has to get
17 involved. At least that would move the ball forward.

18 DR. TUCKSON: I would be surprised if there is
19 anybody here under the reality that we've already moved the
20 ball to the next step that wouldn't think that we don't
21 want to wait for Congress to have to do that. I think your
22 suggestion makes all the sense in the world.

23 Even those that were not in favor of the
24 proposal were all in favor of expeditious. So I think
25 you're talking about jump-starting that, and I think that

1 none of us would disagree that we wouldn't want to say
2 okay, we've got to go to Congress and get permission to do
3 the analysis. No. So I think your point wins the day. I
4 don't see anybody rushing to disagree.

5 DR. FEETHAM: I would just like to remind
6 everyone that HRSA and NIH funded a three-year beginning
7 study on the genetic workforce, which was
8 interdisciplinary, looking at specialists, non-specialists,
9 and primary care providers. If we could build off of that
10 excellence --

11 DR. TUCKSON: That helps. Cindy has that and
12 needs to roll that in. Here is what we're going to do
13 next. We're going to bring this to closure. Here is what
14 happens. I need a reality check from Sarah and Cindy.

15 The reimbursement policy coverage thing has
16 been kicking around now for a good while, and has gotten
17 better every day with all the input. What is our timeline
18 for when we absolutely expect and must have that report go
19 out for public comment?

20 MS. BERRY: Can I ask one thing? I don't know
21 how you want to handle it, whether you want to blow them
22 off or what, but we have two remaining recommendations
23 unrelated to genetic counseling. I think, and I don't want
24 to jinx it, but they're probably in the no-brainer category
25 where we might get some pretty quick consensus.

1 Do you want to turn to those?

2 DR. TUCKSON: I'll suspend it for just a
3 second. Thank you. Thank God you raised it. But just for
4 the moment, what is the timeline of when this report has to
5 go out?

6 MS. CARR: Right away.

7 DR. TUCKSON: Right away is the answer. So in
8 other words, I think what that means, and let me just make
9 sure, does that mean, therefore, that the one thing we are
10 not going to do is to put in the things that we've done
11 today and yesterday, all the work that we've done, and then
12 come back and revisit it at the next meeting? We are
13 actually intending that it goes out before the next
14 meeting?

15 MS. CARR: Well, let me just say, it's always
16 up to you. If the committee doesn't feel that at the end
17 of this meeting they are ready to go out with the report
18 for public comment, we can wait until June. I mean, I
19 think you want to do something. I think your goal was to
20 have the report finished.

21 DR. TUCKSON: All right. Second question.
22 Would you, Cindy, be willing, and again, you tell me about
23 the process, that given how much work we did on that report
24 this meeting, that the committee, subcommittee, redo a last
25 draft on this, and then it will go out before June, but

1 giving folk if they have just any little comment they want
2 to make, you can decide if we use it or not, but you can
3 make sure everybody sees what it is going to be before it
4 goes out for public comment.

5 Knowing again that going out for public comment
6 means just that. It is not absolutely perfect. We're
7 going to get some comments back, and then we'll come back
8 and change it again. I think we're agreeing we're not
9 going to wait until June to send it out.

10 The question I'm asking then specifically is
11 would you object to having people at least send in some
12 email comments on what will be now the last draft?

13 MS. BERRY: That will work.

14 DR. TUCKSON: That will work. Okay. With
15 that, can anybody find their last two recommendations from
16 yesterday? Those, by the way, who are public comment
17 people, I hope none of you have to catch a plane, because
18 we're coming to you, not too many minutes late.

19 MS. BERRY: The last two, it is on the summary
20 document that was in everyone's folders. They deal with
21 the broader issues.

22 Just to summarize the first one pertaining to
23 provider education and training, it addresses the fact that
24 there is a lot more work that needs to be done in making
25 sure that the current medical workforce is adequately

1 schooled in genetics and genomics such that they can
2 provide the requisite care to their patients.

3 So this recommendation essentially pulls from
4 something that was recommended to the Secretary last year.

5 You can read it. It basically asks the Secretary to
6 develop a plan for HHS agencies to work with state,
7 federal, and private organizations essentially to help
8 medical professionals so that they have the tools they
9 need. It also urges the Secretary to incorporate genetics
10 and genomics into HHS initiatives. That's the first one
11 with regard to education and training.

12 DR. TUCKSON: Does anybody have any big issues
13 with that?

14 DR. WILLARD: I move we accept it.

15 DR. TUCKSON: Going? Going? Going?

16 (No response.)

17 DR. TUCKSON: Done. Next?

18 MS. BERRY: All right. The last one. Public
19 awareness recognizes the lack of knowledge or complete
20 information available to the public with regard to genetics
21 and genomics. States the fact that we need to get out to
22 the public reliable and trustworthy information about
23 genetic technologies.

24 It talks about the development of performance
25 and efficiency measures based upon evidence-based clinical

1 guidelines that would better enable consumers and patients
2 to evaluate health plans and health providers.

3 Now, it's sort of vague and fuzzy. I don't
4 know if we want to be more specific than that. It really
5 doesn't say who will develop these things. It would be
6 good to get some input from members of the committee as to
7 what we might suggest here.

8 DR. WILLARD: This one doesn't actually read
9 like a recommendation. It is just a statement of
10 motherhood and apple pie, which is fine as a statement.
11 That's actually in the text. We're not actually making a
12 recommendation to have the Secretary do anything. So I'm
13 not sure we actually need it. The text I think stands
14 pretty well by itself.

15 DR. TUCKSON: Yes?

16 DR. KHOURY: The only thing that might apply to
17 HHS is to provide direct recommendations about initiatives
18 like the Surgeon General Family History Initiative, which
19 is something that HHS is spearheading anyway to encourage,
20 suggest, or whatever language you want to use.

21 By the way, if such a recommendation is
22 changed, I would suggest to add the words "family history"
23 somewhere.

24 DR. TUCKSON: Well, I think what this is
25 getting at, I mean, I think everyone understands it, but

1 again, this is the consumerism movement where now people
2 are having to make more choices that are financial risks
3 for them about where they go for care, and the nature of
4 the benefit packages that they are offered.

5 So what this is sort of getting at is saying I
6 think what the recommendation would be, Hunt, is be more
7 around the Secretary of Health making available through
8 government Internet websites, information that helps a
9 person make better and more informed choices in this
10 regard.

11 Including family history would be part of it.
12 So I'm one of the people that are addicted to the National
13 Library of Medicine website.

14 DR. FITZGERALD: PubMed.

15 DR. TUCKSON: PubMed, that's it. So in other
16 words, the Secretary would sort of help make sure that this
17 kind of information was on a PubMed kind of site.

18 DR. WILLARD: But do we have enough
19 information? At least I don't feel I have enough
20 information to say whether that should be the Surgeon
21 General's site, or it should be a CDC site, or any other
22 site.

23 DR. KHOURY: It should not matter as far as
24 this committee. You ask HHS to do it, and then we figure
25 it out.

1 DR. TUCKSON: So you are saying use such
2 resources to make this information available to the public.
3 Guidance and education to the public. That is what this
4 is getting at.

5 So with that as perhaps a friendly amendment,
6 we would urge the Secretary to make HHS resources
7 appropriately available to guide people in making these
8 kinds of choices and decisions. Okay, done.

9 We are going to conclude this and move to the
10 public comment. Let me just say this. Let me ask one
11 favor of you in terms of the report that Cindy sends back
12 out.

13 It would be this. Normally I'm not a big fan
14 of people who if you send them an email to a multiple list,
15 and then they've got to tell you yes and send it to
16 everybody so that you've got 1,000 emails that don't make
17 sense. In this case, I think it does make sense that if
18 you make a comment on the report, you might want to click
19 everybody, so everybody sees the comments that are going
20 back and forth.

21 At the end of the day, Cindy and the committee
22 have the responsibility for taking that stuff and weaving
23 it into a final document. But I think in this case it is
24 probably better that we all sort of share our thinking and
25 thoughts. But you don't get to reargue the issue, that's

1 the only thing. The issue is resolved. Now the question
2 is how do we do it?

3 You all are terrific. You guys are a terrific
4 committee. Even when people don't agree, you work
5 together. You are a model of democracy.

6 Public comment -- speaking of democracy --
7 Susan Manley, National Society of Genetic Counselors. I
8 want you to sit right there. Head of the table. They'll
9 make the microphone work.

10 MS. MANLEY: I thought this would be good
11 timing. Good afternoon. I'm Susan Manley, Chair of the
12 Professional Issues Committee within the National Society
13 of Genetic Counselors.

14 As you know, NSGC represents over 2,000 member
15 genetic counselors practicing in a variety of medical
16 specialties, providing genetic counseling in prenatal,
17 pediatric, and adult settings, as well as working in
18 academia, research, and biotechnology companies.

19 NSGC would like to thank this committee for
20 taking our previous testimonies and information into
21 account when developing draft resolutions and reports, and
22 we would like to continue to have input where appropriate
23 as SACGHS moves forward with the important issues discussed
24 at this meeting. Primarily billing and reimbursement for
25 genetic counseling services and the development of

1 population-based genetic databases.

2 With regards to reimbursement and coverage
3 issues, as you heard yesterday, genetic counselors are
4 uniquely qualified to provide genetic counseling services.

5 But without reimbursement for these services, the public's
6 access to appropriate genetic services faces a limited
7 future.

8 It is critical to note that Masters trained
9 genetic counselors currently make up over 50 percent of
10 practicing genetic specialists, which means that genetic
11 counselors are currently providing the majority of genetic
12 counseling services, and will likely continue to do so in
13 the future.

14 Although additional studies must be done to
15 clearly define the value and cost-effectiveness of genetic
16 counseling services as conducted by specific providers,
17 there are already many examples cited by the working group
18 on genetic counseling services through invited testimony
19 yesterday.

20 The issue of reimbursement for genetic
21 counseling services and in particular, those provided by
22 Masters level genetic counselors, is critical when we
23 consider the impact on the genetics workforce.
24 Specifically, if genetic counseling services provided by
25 genetic counselors and other non-physician service

1 providers are not reimbursed, it will continue to impact
2 access to quality services nationally.

3 This committee is in the position to make
4 recommendations regarding the future of genetic services in
5 health care. Currently, the educational and credentialing
6 structure exists to produce quality, certified genetics
7 professionals. However, without adequate reimbursement,
8 public health could be compromised by the provision of
9 increasingly available genetic services by uninformed
10 health care providers without specialized training.

11 As was proposed yesterday by the working group,
12 the NSGC appreciates the support of this committee, and
13 strongly encourages you to continue to develop
14 recommendations that explicitly support the recognition of
15 non-physician genetic services providers, specifically
16 including Masters trained genetic counselors who hold
17 credentials that document knowledge in human genetics and
18 clinical genetics expertise.

19 We also hope that SACGHS will advocate in all
20 matters appropriate for the development of CPT coding that
21 is specific to credentialed genetic counseling service
22 providers, and for both third party payers and CMS to
23 recognize the importance of reimbursement and coverage for
24 genetic counseling services by appropriate providers.

25 Lastly, SACGHS can recommend that studies be

1 funded to continue to assess the value and cost-
2 effectiveness of genetic counseling provided by
3 non-physicians.

4 With reimbursement, qualified genetic
5 counseling providers can become even more valuable in the
6 financial realm of U.S. health care, and allow more medical
7 facilities to offer quality genetic services to the public.

8 Finally, the National Society of Genetic
9 Counselors applauds SACGHS for considering the logistical
10 and ethical issues associated with large population-based
11 genetic studies. Many of our members work in research
12 genetic settings, functioning as research coordinators,
13 including the provision of informed consent.

14 NSGC members recognize that the scientific data
15 that arises from population-based studies will have a
16 powerful impact on the data that is available to provide
17 clinical information to patients in the future.

18 DR. TUCKSON: Thank you. Susan, that's
19 terrific. I just would say that that's a very important
20 statement. So now given where the committee is, I really,
21 really hope, at least as the Chair of the committee, that
22 your community now will take the initiative and really move
23 forward and provide very detailed and very explicit
24 suggestions into the public discourse around how you
25 actually now accomplish this certification.

1 Not just for the small groups that have it.
2 You've got to really figure out how that is going to work.
3 You have heard us about 12 times say that there are some
4 fundamental questions that need to be dealt with and
5 answered. You guys have opinions about it, and you
6 probably know others, but I think the ball is really now
7 back in your court in your community to respect the
8 professionalism of what you do and figure this thing out
9 and make those suggestions.

10 I really appreciate your comments. As I say,
11 now you threw it at us, and we ran with it. Now the
12 question is you all are going to have a lot of work to do.
13 I know that is what you wanted.

14 MS. MANLEY: And we know that already as well.

15 DR. TUCKSON: I figured that. Susan, you have
16 been terrific. Thank you so much.

17 MS. MANLEY: Thank you.

18 DR. TUCKSON: Greg Rapp? Greg? I'm sorry.
19 Please come right in and introduce yourself for the record.

20 MS. MENSCH: My name is Stephanie Mensch. I'm a
21 consultant to AdvaMed, the Advanced Medical Technology
22 Association. AdvaMed represents manufacturers of
23 diagnostic and genetic tests, among other medical devices,
24 which is why we are interested in the activities of this
25 committee.

1 We'd like to thank you first for the
2 opportunity to make comments during this session. We're
3 very pleased with the amount of time that you've spent
4 deliberating on issues that our members consider to be very
5 important relating to the coverage and reimbursement of
6 genetic tests.

7 We do believe that for the tests themselves,
8 how Medicare treats them will have an impact on access. We
9 understand that there are certain limitations in terms of
10 prevention and information in how the agency views these
11 tests, and what they are used for.

12 We do appreciate the amount of time and effort
13 that this committee has put into understanding the issues.
14 Hopefully your report will be a major source of support to
15 move this forward through Medicare and other agencies that
16 are related.

17 We did submit specific comments, almost line by
18 line comments in September, and appreciate how much work
19 has been done since then on the draft. We do look forward
20 to doing a very careful review of the report when it comes
21 out for public comment in the next few months.

22 What I passed around is AdvaMed's policy
23 statement on another section of the Medicare Modernization
24 Act, which we hope that you'll also address in your report,
25 even if it is just to acknowledge to CMS that you are

1 interested in how they are implementing this section of the
2 report. It has to do with how new tests are paid under the
3 clinical lab fee schedule.

4 You did mention the MMA provision having to do
5 with coverage in the report, but this is Section 942. It
6 also talks about the disposition of new tests. It puts
7 into place a very thoughtful process. A public, open,
8 transparent process. We think this is important because we
9 would like to be sure that the agency and the contractors
10 in the field who may be doing gap filling understand
11 completely what is required of them to develop cost data
12 for new tests, and that this information, the data is made
13 public.

14 AdvaMed has summarized what is in the law
15 itself at the beginning of the policy statement, but also
16 because the statute is fairly broad as it is written, we
17 have offered our suggestions for additional regulatory
18 provisions that we believe can be implemented on the
19 regulatory level.

20 There was an open meeting, a town hall meeting,
21 that CMS held in January to take comments. We provided our
22 comments to CMS at that time on new tests, on implementing
23 this section. It is our understanding that a notice of
24 proposed regulation will come out in late spring or early
25 summer to implement these provisions. So the timing of

1 your final report will be right on time if you were to just
2 mention that you are interested in how CMS is carrying out
3 this provision of the law.

4 I think that that is pretty much what we're
5 asking for, is to just have your recognition that these
6 provisions are important, and that some stakeholders, like
7 AdvaMed and others, in the lab community are very
8 interested in being able to have the best that we can get
9 for new tests, understanding the limits of the current
10 Medicare fee schedule.

11 Again, thank you for this opportunity to
12 comment. We hope that you will consider making a
13 recommendation in your final report that relates to
14 implementing the new test section as well.

15 Thank you.

16 DR. TUCKSON: Thank you very much. Let me also
17 thank you all for a very well done briefing paper. One
18 page, front and back. Very specific, absolutely right to
19 the point on every point you're making. We understand the
20 point that you're making very clearly. Obviously a lot of
21 work went into this. I think it stands on its own. We
22 have this, and we will certainly study it.

23 Does anybody have a question?

24 (No response.)

25 DR. TUCKSON: Again, very well done. Thank you

1 very much.

2 MS. MENSCH: Thank you.

3 DR. TUCKSON: Maureen Smith from NUGene
4 Project, Center for Genetic Medicine, Northwestern
5 University.

6 MS. SMITH: Good afternoon. I'd like to take
7 us back to the topic from this morning on large population
8 studies. I represent the NUGene project, which is a
9 genetic banking study conducted at Northwestern University
10 in Chicago, Illinois. The NUGene project is a
11 population-based initiative whose purpose is to develop a
12 diverse collection of samples and information that will
13 facilitate biomedical research on the genetic and
14 environmental factors contributing to health and disease.

15 NUGene currently combines a centralized genomic
16 DNA sample collection and storage system with the ability
17 to regularly update participant's health status and
18 retrospective and prospective data from electronic medical
19 records. The project received initial seed funding from
20 the Northwestern University and its health care partners.

21 I will shorten my statements, as this has been
22 fairly extensively discussed this morning. I just wanted
23 to make a few points.

24 One is the NUGene study is conducted throughout
25 the Northwestern Health Care System, which includes five

1 hospitals and numerous outpatient clinical sites throughout
2 the Chicago area. We are an approved IRB study through the
3 Northwestern University IRB, and we have a certificate of
4 confidentiality from the NIH.

5 I did want to point out that we have spent time
6 since the inception of this study in early 2002, up until
7 the present time, and continue to work very closely with
8 our IRB. It has been a very lengthy process of education
9 and work, so I wanted to point out that I think it does
10 take a huge effort to educate IRBs about this type of
11 research.

12 Our recruitment began in late November 2002,
13 and we had very modest initial accrual goals so that we
14 might better understand how to best educate and work with
15 our physician and participant populations, as well as to
16 evaluate how to improve recruitment in our informed
17 consenting processes.

18 We have found people to be responsive to
19 learning about the study, and agreeing to participate.
20 However, that certainly does vary given the situation in
21 which participants are approached. But while the public
22 appears interested in participation in studies of this
23 type, we are aware of the need to continuously examine the
24 ethical, legal, and social issues associated with
25 acquiring, maintaining, and managing personal health and

1 genetic information as a large resource.

2 Therefore, we recently served as the site for
3 the Department of Energy-funded ELSI study of informed
4 consent for population-based genetic research. This
5 project assessed the participant knowledge of our study
6 with the goal of improving the informed consent process for
7 large population research. Results of this study have been
8 presented at scientific meetings, and we are in the process
9 of publishing that data.

10 The longitudinal and population-based design of
11 this study positions NUGene, as well as similar studies, to
12 be a resource for a breadth of studies, and I won't go into
13 those, as they were extensively discussed this morning.

14 We believe that our project has begun to
15 demonstrate the value of such collections for research, as
16 over the past six months, being even a small population
17 study, we have distributed samples for three different
18 research studies within our university. These
19 investigations included such varied and common conditions
20 as aneurisms, neural tube defects, and head, neck, and lung
21 cancer.

22 In conclusion, we believe that large population
23 studies will offer great benefits to society, and will
24 enhance our understanding of how environment, lifestyle,
25 genetic, and other factors contribute to health and

1 disease. The experiences and expertise of existing
2 population studies in the U.S., particularly in the areas
3 of informed consent, building sophisticated data
4 management, and sample storage systems, developing privacy
5 policies, and establishing community trust can be leveraged
6 to provide a framework and guidelines for further studies.

7 As others in the international community work
8 to create country-specific, longitudinal population
9 cohorts, we believe that preexisting U.S.-based population
10 repositories should be further developed into a national,
11 not-for-profit consortium.

12 DR. TUCKSON: Well, thank you very much,
13 Maureen, for that. Also thank you for letting us know that
14 the NUGene project is available as a resource as we look
15 forward to these issues going forward. I know several of
16 us will probably try to take advantage of that. Thanks for
17 taking the time to make sure that we know what you are
18 doing.

19 MS. SMITH: Thank you.

20 DR. TUCKSON: We appreciate it.

21 Finally, Mary Steele Williams, the Association
22 of Molecular Pathology. Welcome.

23 MS. WILLIAMS: Thank you. I'll need to provide
24 a new written document to Sarah based on yesterday's
25 discussions. The verbal comments are a little bit

1 different from the document that I provided you with
2 earlier.

3 Dr. Tuckson, members of the committee, good
4 afternoon. My name is Mary Williams, and I am the
5 Director of Scientific Programs of the Association for
6 Molecular Pathology. I speak to you today as a
7 representative of AMP.

8 The Association for Molecular Pathology is an
9 international not-for-profit educational society
10 representing over 1,200 physicians, doctoral scientists,
11 and other professionals who perform molecular and genetic
12 testing, as well as other tests based on nucleic acid
13 technology.

14 The AMP membership is from a wide variety of
15 health care settings, both public and private, as well as
16 from the IVD industry. AMP members are involved in every
17 aspect of genetic testing, research, and education.

18 My purpose today is to provide comments on
19 several issues currently under consideration by the SACGHS.

20 First, review of molecular CPT code reimbursement. AMP
21 strongly supports the proposal in the coverage and
22 reimbursement document to request CMS to review and revise
23 reimbursement for molecular CPT codes.

24 As the number of available genetic tests and
25 their use in routine diagnostics grows, laboratories will

1 not be able to continue absorbing the losses associated
2 with genetic testing as they do today. We strongly support
3 the SACGHS recommendation for CMS to review and revise
4 reimbursement for molecular CPT codes. AMP, through its
5 resources and knowledge of this subject, stands ready to
6 assist CMS in carrying out this recommendation.

7 Second, change in the definition of a genetic
8 test. AMP's position remains in strong support of the
9 limitation in the definition of a genetic test to
10 inheritable germline variations, and not including somatic
11 variations. If a genetic test is more broadly defined as
12 any molecular biology-based test, then there needs to be a
13 distinction that allows for the discussion of the ethical,
14 social, and regulatory issues to inheritable genetic tests
15 separate from testing for somatic mutations.

16 This distinction is not relevant to the
17 coverage and reimbursement report, but may be relevant to
18 future reports of the SACGHS.

19 Third, better coverage and reimbursement for
20 genetic counseling services. AMP in performing genetic
21 tests works closely with genetic counselors and medical
22 geneticists. These professionals provide essential genetic
23 services to patients and their families that are time
24 intensive, and are not adequately reimbursed. AMP strongly
25 supports a recommendation to define genetic counselors as

1 allied health professionals allowed to direct bill, and to
2 review the billing codes associated with genetic counseling
3 services.

4 Last, gene patents. AMP asks that SACGHS give
5 full consideration the negative impact of exclusive
6 licensing and enforcement practices for gene patents on the
7 future of genetic testing. We understand that SACGHS has
8 set this as a high priority, but has decided to wait for
9 the National Academy of Sciences' study of intellectual
10 property related to genomics and proteomics.

11 We urge you to promptly set this as an agenda
12 for the SACGHS as soon as the report is available. On
13 behalf of AMP, I thank you for the opportunity to speak
14 with you today. AMP remains available to the SACGHS to
15 assist with or provide information for your thoughtful
16 deliberations and important work.

17 DR. TUCKSON: Mary, thank you very much.
18 Thanks for making sure that we are staying closely
19 connected with the association. That's important that you
20 are clearly with us as we go forward.

21 The patent thing we talked about yesterday, and
22 we are right on board there. We are waiting for the NAS
23 report as well.

24 We don't have a lot of time, but I just wanted
25 to note in terms of I appreciated the guidance around the

1 laboratory testing thing. I'm not sure what we might do
2 with that comment right now, other than we'll take it as
3 you've made a point. We have to deal with it at some
4 point. So we'll probably get back to it.

5 Thank you. Good job.

6 We're going to move forward and invite Dr.
7 Joseph Boone, Assistant Director for Science, Division of
8 Laboratory Services, CDC, and Steve Groft, Director of NIH
9 Office of Rare Diseases, as they help us to look at the
10 issue of the summary report from the Conference on
11 Promoting Quality Laboratory Testing for Rare Diseases.
12 You will remember that they had this conference in Atlanta
13 in May of '04. They are making plans for a second
14 conference. The executive summary of the proceedings is in
15 Tab 5 of the briefing book.

16 While the conference was conceived as a plan to
17 address access in quality of laboratory testing issues for
18 rare genetic diseases or conditions, it wound up
19 identifying a number of issues beyond the quality
20 assurance. The group soon expanded the conference to
21 include other topics of interest, many of which intersect
22 with the interest of this committee. Therefore, we will be
23 learning about that and seeing how it dovetails with our
24 activity.

25 Thanks a lot, Joe.

1 DR. BOONE: Thanks very much.

2 It is unfortunate that Dr. McCabe is not here,
3 because some of the things that we're going to be
4 presenting are certainly relevant to this precursor of this
5 committee. We are really addressing some of the issues
6 that have been raised before. Particularly the issue of
7 translation of research findings in clinical practice, and
8 the issue of access in quality of laboratory services.

9 As Dr. Tuckson mentioned, we did have a
10 conference in May of 2004. That conference did address
11 primarily a set of issues that was raised by this committee
12 previously. It has partners, Emory University, NIH, and
13 CDC. That's the reason that we're doing this tag team
14 presentation today.

15 Our definition of quality was really in terms
16 of CLIA. We felt like at least the minimum requirements
17 should be a certified laboratory. So the two areas where
18 we were most concerned were research-only laboratories, and
19 those laboratories that are located outside of the U.S.,
20 and the quality of the services that they might be
21 providing to U.S. citizens.

22 So the basic things that we were looking at was
23 to ensure the quality of access testing, and we were
24 concerned about the research laboratories that might be
25 providing patient testing without a CLIA certificate. We

1 were also concerned about the translation of gene findings
2 in clinical practice. We had a number of other issues that
3 were concerned about.

4 You have these charts in your books, but the
5 main thing is that in terms of the U.S., 78 percent of the
6 tests are being done in the U.S., 22 percent are being sent
7 outside of the country, and 33 percent of the testing on
8 gene tests are for research-only laboratories. That's the
9 test themselves.

10 If you look at the distribution of
11 laboratories, research-only laboratories account for about
12 40 percent of the U.S. laboratories in GeneTests. Non-U.S.
13 laboratories count for 30 percent of all the labs listed in
14 the directory. That was in 2004. The data haven't changed
15 very much since that time.

16 Another thing that's important to look at real
17 quickly is the fact that of the things that are tested for,
18 many of those tests are available from only one laboratory,
19 or from a very small number of laboratories, which makes
20 some of the quality assurance practices that we'd like to
21 have in place difficult to do.

22 There are very few tests that are actually
23 available through the College of American Pathology survey
24 program. Similar in Europe, there are very few tests that
25 are actually being monitored in a quality assurance mode.

1 So in the summary slide, I think the main thing
2 to focus on here is the fact that we're falling further and
3 further behind in terms of development of GeneTests. Rare
4 disease associations are being found at the rate of about
5 20 per month. The new testing that we are able to
6 incorporate is about ten per month. So we're running 50
7 percent behind in terms of developing new tests to address
8 the conditions that are being found in the gene findings.
9 That gap really does need to be closed.

10 So the results of our first conference was that
11 we actually formed a North American Laboratory Network for
12 Rare Disease Genetic Testing. That network is comprised of
13 laboratories that are all CLIA certified, and will report
14 the limitations of the tests in their reports. They are
15 going to work collectively to increase the development of
16 new tests to foster research and clinical laboratory
17 partnerships and serve as a back-up resource for additional
18 tests.

19 There was an organizational meeting, which
20 Steve is going to talk to you about in a moment. But there
21 were about six laboratories that formed this original
22 alliance of testing laboratories.

23 In addition, the American Society of Human
24 Genetics and the Office of Research Protections agreed to
25 provide education to researchers and IRBs, which is

1 something that was really needed. NIH has a pilot program
2 to fund translation of research tests into clinical,
3 applicable tests. That program, we want to see that
4 expanded in a logical manner. Then we plan to have a
5 meeting later this year, which Steve will tell you a little
6 bit about.

7 So we're on a pathway I think that is the right
8 pathway. We're not confused. We know where we're going.
9 Steve is going to tell you a little bit about how we might
10 get there.

11 DR. GROFT: Thank you very much, Joe.

12 You saw the stop lights, red lights, green
13 lights, yellow lights. Sometimes I think we're working all
14 at one time, so we're not sure how we're going to get
15 there. As you will see in the last slide in the
16 presentation, that's even more of the confusion that we're
17 adding into the situation. I'll try to get this moving.

18 We do have a meeting planned on March 17th
19 prior to the American College of Medical Genetics to really
20 start to crystalize and finalize many of the discussions
21 that have been held previously, both at the meeting last
22 year in May at the Centers for Disease Control in Emory
23 University in Atlanta. A number of discussions have been
24 held by a lot of participants since then to look at
25 presenting this at the September, 2005 conference here in

1 Washington.

2 We have been working on identifying major
3 issues in target audiences that need to be at the meeting
4 in September. We'll be looking at the conference agenda,
5 and then assure that there is broad based participation in
6 the meeting in September. We still are in the planning
7 stages, but things are coming together rather nicely.

8 It seems like for the first time we've been
9 able to get many of the major participants who we had to
10 get together to really affect an effort that would have
11 some outcomes that could move forward. We are getting
12 together here finally, so it's good to see.

13 At the conference in September, again, it will
14 be in Washington. It will be a two-day session. We'll
15 have plenary sessions and reviews. And again, we're
16 working all of these issues up that Joe had talked about as
17 far as the vision and other things that we need to discuss
18 to give us direction, movement, and the momentum to move
19 forward.

20 A couple of the issues that we need to work on
21 are trying to establish the priorities for developing
22 genetic tests for rare diseases. There are so many
23 disorders that we could look at and really start to work
24 on. We really have to try to identify those priorities and
25 the criteria for selecting them. It is just an area that

1 we hope to hear from a lot of people on how we're going to
2 go about this.

3 The conditions for the clinical laboratory
4 participation. We currently at the Office of Rare Diseases
5 have a small program with the National Human Genome
6 Research Institute within the Clinical Center to develop
7 these genetic tests for about four rare disorders last year
8 that we did under the direction of Bill Gault, the Clinical
9 Director for the Human Genome Research Institute.

10 This year, we hope to expand that to about 16
11 to maybe 20 more tests that we will develop, mostly for the
12 use of the Intramural Research Program. So we wanted to go
13 forth and start in the intramural program, get some
14 direction, some experiences, and then move possibly into
15 the extramural program.

16 As we were moving forward last year in
17 developing these genetic tests, we came to the conclusion
18 that this was something that is quite capable of being done
19 in the extramural program. Now we are looking for
20 partnerships within the NIH system to expand the whole
21 program to increase the number of genetic tests that are
22 developed for rare disorders.

23 When you have a total of 6,000 or 7,000 rare
24 diseases, it is quite a task. Where do you start? How do
25 you continue? How do you gain the interest? But there

1 certainly has been a lot of interest in seeing this move
2 forward to have the tests move out of the research stage
3 into the stage of clinical accessibility for the public.

4 The next three slides that you have and that
5 are available for anyone who may be looking in through the
6 website, is we've talked about the long-term visions and
7 the short-term visions for what we want to accomplish, and
8 where we want to go, so I won't spend too much time on
9 that. I know the day is drawing to a close, and people
10 have their planes.

11 There are a number of areas that we want to
12 talk about, and we will discuss the successes. How are we
13 going to measure it? How are we going to identify the
14 successes for the patient's families and the providers, as
15 well as the laboratories and the testing groups. Then
16 finally the success of the system and the services that
17 will provide these services to the public.

18 We hope to evaluate whatever success we're able
19 to achieve through pre and post-surveys of the
20 laboratories, the consumers and advocacy groups, the
21 Centers for Medicare and Medicaid Services, and other
22 payers, and then to monitor the tests that will become
23 available, and to monitor the quality of these tests, as
24 well as any adverse events that may occur. That seems to
25 be a major concern these days, as they should be.

1 Then we hope to lift the roadblocks and to
2 remove them to create the models that will generate the
3 energy to move forward towards the solutions. Again, we
4 know there is a lot of passion involving individual rare
5 diseases, but I think we have to look at this in the sense
6 that we are not going to be able to do all rare diseases at
7 one time. We will start in a systematic fashion and
8 continue to move through and to complete as many as are
9 possible at the present time currently that are in the
10 research stage or in the research laboratories.

11 I guess we have been hearing about the need to
12 do this for many years from a lot of the patient advocacy
13 groups who of course would like to have a genetic test
14 available for their disorder.

15 There is always the concern that if they are
16 available from a research laboratory, that the research
17 money will dry up, and the project will just die. It may
18 never be available for use in the clinical services. So I
19 think those are some of the areas that we're looking at,
20 and some of the needs that we're trying to work with as we
21 move forward.

22 This is a slide that we have tried to put
23 together. We could have put all those different lights in
24 there too as well. You see the number of partners that we
25 are dealing with. Actually it has been very nice progress

1 I think as we move forward from the planning last year for
2 the May meeting in Atlanta to where we are today.

3 The number of groups that are involved are
4 numerous, yet there has been a good sense of a need to move
5 forward quickly and as expeditiously as possible. So I
6 think we'll just end it with that one and try to answer any
7 of your questions that you might have.

8 DR. TUCKSON: Thank you both. Very, very
9 important work.

10 The floor is open. Any questions?

11 DR. WILLARD: Just a point of information. Are
12 there precedents or other examples where HHS steps in to
13 prioritize development of tests for diseases that affect,
14 by definition in this case, a very, very small number of
15 its citizens?

16 DR. GROFT: I don't know of any directly,
17 although looking back on when we started with the Orphan
18 Drug Act back in 1983, we tried to identify compounds that
19 were available on the shelves of companies that weren't
20 being developed.

21 We tried to provide incentives. That's what
22 happened through the Orphan Drug Act, incentives. But we
23 also tried to identify compounds that would be useful. We
24 went about then funding research, trying to support
25 research for those areas.

1 So I think the scientists, the laboratory
2 people will identify those. As I mentioned, some of the
3 first areas we'd like to work with are those that are
4 already in the research laboratories, and maybe could move
5 over to the clinical side.

6 DR. BOONE: And we've talked about the federal
7 process, but we also have a private sector process that's
8 engaged in this overall activity with us. There were some
9 50 people that were at our original meeting, and we hope to
10 have maybe as many as a couple hundred people at the
11 September meeting.

12 We get the same message from the people in the
13 private sector, that the rare disease community is coming
14 to them with funds in hand wanting tests developed. They
15 simply don't have enough capacity to move these tests
16 through the system.

17 DR. GROFT: And for the most part, we probably
18 will not establish the priorities completely. I think this
19 is where a community will come forward. We are looking for
20 a cooperative effort among the patient advocacy groups, the
21 laboratories, the NIH, the CDC, and all of the government
22 agencies who have to work together on this issue.

23 So there will be a lot of people coming
24 together. In the last slide, you could point there as to
25 who is going to bring the tests, the need for certain

1 tests, and everyone will be bringing the tests forward to
2 us for consideration. But we will not be the sole source
3 of funding.

4 MS. ZELLMER: I just had a quick question.
5 Just based on what you said then, are primarily then the
6 barriers to getting these tests developed the laboratories
7 just not having the capabilities? Or are they more
8 financial? Or both?

9 DR. BOONE: It's a little of both. I mean, Dr.
10 Ledbetter at Emory University indicates of course there is
11 enough capacity to do these tests within the United States,
12 but some tests are going abroad. You have to ask the
13 question, why is that occurring. I think there are several
14 reasons that that is occurring.

15 I really applaud NIH for taking this initiative
16 to try to put the researcher with the clinical lab in a
17 partnership so that that transition period hopefully will
18 take less time, and we'll be able to move tests more
19 rapidly through.

20 This really is a network that is starting to
21 build, too, because there are a few labs that are in this.

22 If the pilot really works well, then certainly we can
23 engage I think more genetic testing laboratories in this
24 process.

25 DR. GROFT: I think with so many rare

1 disorders, there are so many possible conditions and
2 situations that exist that you can't say it's this or that.
3 There are many, many different possibilities here.

4 But we are hoping to have some pilot projects
5 involving different laboratories so we gain the experiences
6 of commercial laboratories, as well as CLIA-certified
7 laboratories, some that are in so-called ultra-orphan
8 disorders with a very, very small prevalence of diseases
9 that we'll look at to see how things are done and how we
10 might be able to just use those experiences to extend out
11 to the entire community.

12 DR. TUCKSON: Thank you both. We very much
13 appreciate it. We look forward to updates after the
14 meeting. Thank you both.

15 All right. We are just going to have a couple
16 of minutes, and then we know that some of you really need
17 to get out of here, so we're going to end a little early, I
18 think.

19 Let me summarize a couple of things I think
20 that we said that we would do. This is not going to come
21 out real well, because I thought I was going to have a few
22 more minutes to actually sort of organize this.

23 Anyway, the main thing is that Sarah knows what
24 we're supposed to do. On the genetic discrimination
25 discussion, before you go, Muin, because there is something

1 that says you were supposed to do something. On the
2 genetic discrimination, we are going to do the DVD. I did
3 that narration this morning. So we have approved the
4 script, and that is moving forward.

5 The public comments to the Secretary are being
6 collected, and those will go forward to the Secretary. The
7 legal analysis, we are not going to wait for the legal
8 analysis to get done. But in the body of the letter to the
9 Secretary, we are going to urge the Secretary to use all of
10 his influence to expedite the legal analysis from the
11 various departments and everyone that is involved with
12 that. Then we are requesting that the Secretary hold the
13 stakeholder meeting to help broker any differences that may
14 exist in that community to move that forward. So those are
15 the things that we agreed to on the genetic discrimination.

16 On the health informatics infrastructure, I
17 think we wanted to send a letter to Brailer saying thank
18 you, and urging again that we want them to remember what we
19 are trying to do here, the family history issues in
20 genetics being important as he unveiled his strategic plan.

21 Muin is to work with Alan Guttmacher and/or Frances to
22 draft the letter in fact to Brailer.

23 That's what you're doing. You already did it.

24 DR. KHOURY: No, actually, we talked with Alan
25 yesterday. So I think Alan is taking the lead on behalf of

1 all of us, and we'll contribute.

2 DR. LESHAN: We'll work with you.

3 DR. TUCKSON: Oh, it's the old wait for Alan to
4 leave, and then give him the assignment. That will teach
5 you all to leave.

6 For whatever the Rodney Howell committee, what
7 is it called?

8 MS. CARR: Heritable Disorders.

9 DR. TUCKSON: Heritable Disorders. Any of you
10 that have comments that you want reflected there, go to Joe
11 so that Joe Telfair can carry the water for us on that
12 committee.

13 On the reimbursement, I'm not going to
14 summarize that again. If you all didn't get that the last
15 time, shame on you. So I want to also just -- large pop?

16 MS. CARR: Yes. On large population studies,
17 we are writing a letter to the Secretary with a number of
18 points that we're going to make.

19 DR. TUCKSON: All right. So we've got the
20 large pop. That's exactly right. So we've got that.
21 That's in our notes.

22 I want to welcome again to the committee Joe
23 Telfair. I thought Joe was terrific. What a terrific
24 addition to the committee.

25 Kevin, we'll just wait for him to leave, and

1 then we'll say nice things about him.

2 (Laughter.)

3 DR. TUCKSON: But Kevin, really welcome.

4 I just think this is really fun. What a good
5 group.

6 I think all of you would join me, by the way,
7 and the ex officios, thank you all very much for coming,
8 and all the contributions that the ex officios made. It is
9 terrific.

10 The webcast people, thank you all for that.
11 Again, there are a lot of people out there that care about
12 this. So thank you for that.

13 Thanks to the soundman. You were terrific
14 keeping us on track.

15 Sarah and the team, always just stellar behind
16 the scenes. Every single person is to be commended.

17 (Applause.)

18 DR. TUCKSON: Now, the people that deserve the
19 biggest applause are the audience. I mean, how they can
20 sit through this stuff?

21 (Applause.)

22 DR. TUCKSON: And they don't get to talk and
23 just have to be talked at. But we really appreciate your
24 involvement and expertise.

25 Does any member of the committee have any last

1 words?

2 MS. HARRISON: I have one last comment. I
3 think I always say this at the end of the meeting. I still
4 want to at least keep in our minds that we do have a duty
5 to the public to let them know about our proceedings and
6 things that are going on, and that the Federal Register may
7 not be the best place. So I think we still have a duty.

8 DR. TUCKSON: Which I'll piggyback on also.
9 Again, that comment that I made at the beginning of the
10 meeting, I still want us to somehow, even though we've got
11 a lot on our plate, how do we get at this education of the
12 American public? Not just even about, although it is
13 important what you are saying, it stands on its own about
14 what we are doing, but it is educating the public around
15 these issues.

16 I think that's important. I'm glad we got it
17 into the recommendation at the end for the Secretary on the
18 coverage and reimbursement issue, where we can start to get
19 the Secretary using the information distribution mechanisms
20 at his disposal to try to educate people about these
21 things. I think that's important, so I'm just piggybacking
22 on that.

23 Does anybody else have a comment?

24 (No response.)

25 DR. TUCKSON: Well, with that, it was a hard

1 two days. Good for you all. Thanks a lot.

2 (Whereupon, at 3:47 p.m., the meeting was

3 adjourned.)