DEPARTMENT OF HEALTH AND HUMAN SERVICES

SECRETARY'S ADVISORY COMMITTEE ON GENETICS, HEALTH, AND SOCIETY (SACGHS)

- Sixteenth Meeting -

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Tuesday

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Hubert H. Humphrey Building
200 Independence Ave., SW
Washington, DC

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C O N T E N T S

C O N T E N T S *(continued)*

P R O C E E D I N G S

[8:05 a.m.]

Opening Remarks

Steven Teutsch, M.D., M.P.H, Chair

DR. TEUTSCH: Good morning, everyone. Welcome back. We had an interesting session yesterday. Rick and I were just comparing notes about yesterday afternoon's session and the opportunity to continue that discussion this morning.

Before we get into that discussion, I want to introduce, for those of you who may not know him, our regular and close friend of the Committee, Rick Campanelli, who is the counselor for science and health policy here in the Department. I say he is a close friend because he is the man who helps us with carrying the message to the Secretary and helping us get our work done in an effective way. We are always appreciative of his support and always delighted to see him here.

Rick is here today on a bittersweet mission, so let me turn it over to you, Rick.

Presentation of Award to Dr. Francis Collins

Richard Campanelli, J.D.

DR. CAMPANELLI: The bittersweet mission is to say a few words on behalf of a person who is a friend to me and to all of us. The occasion is Francis Collins' departure from SACGHS. I thought I should be at the podium to do that, so I had to come up here.

It is great to be with you all again. It was very interesting, wasn't it, to be with many of you yesterday for the discussion about the intersection of consumer health and consumer access to information and genomic medicine. I know that you are going to continue that today.

I have had a chance to visit with you up here a number of times on substantive issues but most recently on the occasion of Reed Tuckson's departure from the Committee and now on the occasion of Francis Collins' departure from the Committee. I don't want you to think that every time I come somebody is departing.

[Laughter.]

DR. CAMPANELLI: It could be a bad sign.

But it is not. I really hope that is not true because we very much appreciate and recognize the importance of your work and are grateful for it and all

of your involvement and the time you are committing.

I do have the honor today, on behalf of Secretary Leavitt and all of my colleagues at the Department, to say thank you to you, Francis, for your service to this community for many, many years. I should probably just say many years, not many, many, although it is true.

Francis, in recent weeks with the passage of GINA we have had the chance to recognize your important contributions in advocating for patient protections that ultimately resulted in the passage of GINA. If we had known that shortly after it passed you would be announcing your departure from the Department, we may have left a few wrinkles in there that would require you to stay on longer or maybe not work so hard.

Actually, it was a great effort for many years on behalf of many people. I know Francis recognizes that. But especially, Francis, you and your team, and you personally, made a great contribution and really helped to push that toward the end. It took a great concerted effort, as you and I both know, to get the ball over the goal line, and to good effect.

All of us know as well, though, that our debt of gratitude to Francis goes far beyond GINA, as important as that is. You shaped the vision of the Human Genome Project, and with your team at NHGRI and NIH you advanced science achievements that have unlocked and will continue to unlock so much potential for improving human health.

That phrase, "unlocking and continuing to unlock so much potential for human health," that is an audacious statement. It is amazing because it is true. Sometimes you say things like that, but I was just rolling that thing around in my mind.

I remember the first time we met. I had the privilege of sitting in your office, and I really felt it a privilege, as I do now, to have sat in your office, as you walked me through where things were with genomic research and where things were at NHGRI.

At one point you got that smile on your face that I know we all recognize -- that you have right now -- and that I have come to see so often when you talk about your work. I have often thought that that is the smile of the joy of the privilege of great discovery.

You see it on the faces of little children a lot when they discover things, but you don't often see it on the faces of sophisticated adults and great scientists. It is something that I think all of us can really emulate and look to, the joy that you have had in your work.

Francis, with you it is contagious. It is hard not to smile back. You said to me then that in years to come people will look back on this era of unlocking the genome as the ushering in of a whole new era in science, perhaps unmatched in the history of medicine. You weren't talking about your accomplishments but about what it meant for all of us for how we view health care.

Just yesterday I was talking with one of the leaders of the new Scripps Medical School, an institution not even open yet, where the curriculum will fully integrate genomic science and throughout the curriculum. They are the leading edge, perhaps, of the next generation of doctors, prepared to bring these results to the bedside, a new army being formed, prepared to fight disease and sickness with new weapons, weapons which you helped to give them.

This is a wonderful gift that you have given

all of us, but there is something that is just as significant as the discoveries themselves. In all of these wonderful discoveries you have kept insight and become a recognized voice for making sure that science and scientists consider all of the important issues and steps as they pursue their path. GINA is one of those examples.

But in addition, you have become, and we will trust you will continue to be, a voice that ensures that ethical issues remain at the forefront as we pursue the wonderful science that is upon us.

Recently, I was at a dinner with a person pretty high up in the government of the EU. He had an important leadership position and was involved in some controversial aspects of human molecular research that has been in the press. At one point he was enthusiastically describing some of these things. I asked in a gentle way how is it that he was able to integrate the significant moral and ethical debate in the effort of pursuing science there.

This is what he did. He turned his face sideways away and waved his hand in a big arc, and then

just continued with the scientific discussion. So the scientific discussion went on, and it was very interesting and very valuable, and we engaged in that scientific discussion.

Then he said, "But I don't think you could do a lot of this in the U.S." It seemed to me a natural question, so I said -- and this is why you don't want to invite me to dinner -- "Well, how is it, then, that you deal with or integrate the significant moral and ethical questions?" He turned his head away and waved his hand.

Francis, you have contributed so much to science. No one can deny it. Just as importantly, your life and voice have reminded all of us that we can and must always be able to entertain these important questions even as we are fully engaged in excellent science. You have kept the big picture of health and the ways that science and technology is applied to it in mind, and in so doing you have enriched our science and our public debate.

Not only are you open to true scientific inquiry and debate, but you are a really good debater. I know. I have had the privilege of engaging in and

learning from you at the intersections of policy and law, and some recently. It has always been a joy and it has always been a great education for me. It has been one of the wonderful privileges of my time as counselor to the Secretary.

Fifteen years is a long time at anything, and I am sure that over the next week there will be many attempts to tell the Francis Story, and there should be. Your work and contributions to this Committee have had a remarkable influence. Now, after many reports, meetings, and conference calls, at the end of this particular journey I think all of us can acknowledge that you have helped take us to a new land with an appreciation for science and the benefits of what it means for those who follow.

We here want to acknowledge your many valuable contributions, and I want to say thank you on behalf of the Secretary and the Department. We thank you for bringing together the discipline and mind of a great scientist and especially bringing it together with the joy and the exuberance of a boy on the edge of a great adventure. Thank you very much.

[Applause.]

DR. TEUTSCH: Before I allow you to say something, I want to say a few words on behalf of the Committee as well. I haven't known you as long as Rick has, but nonetheless, from a distance it has been extraordinary to see all that you have accomplished.

Yesterday we talked about the things that have happened over the last few months that this Committee is proud of, and we talked about those events: reports that have gone to Rick and the Secretary which we hope will have an impact. But the one thing we didn't talk about, and perhaps the biggest of those events of course, is the amazing news of the next steps in your career, or what we hope to learn about them and the accomplishments that you have going forward.

DR. COLLINS: I hope to learn, too.

[Laughter.]

DR. TEUTSCH: I wasn't here when these committees were created, but I understand fully that you were the pivotal person who recognized the importance of advisory groups and that helped to create the Advisory Committee on Genomic Testing and now this Committee.

It has been important to us that this Committee has been able to tackle some of the complex issues that you have been facing for your entire career. We very much appreciate all the wisdom that you have brought to us and to the country and the kind of scientific leadership that you represent. It is the kind of thing that we hope will continue to be fostered here in the Government, and we know that you are going to go on to great new achievements.

On behalf of the Committee, though, we do hope that you will stay with us, that you will be a member ex officio emeritus so that we can continue to benefit from all your ideas and suggestions.

As a token, we wanted to present you with this gift, which we hope you will find to be a fitting symbol of your extraordinary leadership and vision as you move forward to the next steps in your career.

While this is surely not the first, nor will it be the last star that you have received, we want you to be assured that this one comes with the Committee's enduring respect, gratitude, best wishes, and admiration. So, many thanks to you.

[Applause.]

DR. COLLINS: Since I'm still a government employee, I assume this is all entirely okay with all of our various rules.

DR. TEUTSCH: Yes, we have had it fully vetted.

[Presentation of award to Dr. Collins.]

DR. COLLINS: Oh, wow. My goodness. How beautiful. Thank you all.

[Applause.]

DR. COLLINS: Well, I didn't expect this at all. I guess it is a good thing I didn't show up late this morning.

[Laughter.]

Remarks by Dr. Francis Collins

DR. COLLINS: Having been in a different time zone for the last few days, there was a serious possibility of missing the alarm going off. But I'm really glad to have made it here in time for these really very unexpected and wonderfully comforting words from both of you.

This decision of mine to decide to move on to the white space of unemployment has not been arrived at

easily, but after 15 years of this incredible privilege of having a chance to stand at the helm of the Genome Institute I felt it was time to seek some other opportunity to serve in a way that is yet to be defined, for several reasons.

One is, it is really difficult as an NIH institute director to do much in the way of a serious exploration of next opportunities without bumping into potential conflicts of interest. It seemed more reasonable to step out into a place where those would not apply and do a more leisurely kind of search, hoping at the same time not to run out of grocery money.

It also is going to give me a chance, I think, to do some reflection about where we have come from and where we may be going and what are the next opportunities that I might be most usefully able to contribute to.

I could talk for a long time about the way in which this particular Committee, the SACGHS, and its predecessors occupy a critical place for the deliberation on the issues that are so near and dear to my heart and to all of you who are putting your time into this.

I have to say, Rick, it has just been

delightful and wonderful, with your arrival on the scene, to have such a comrade of serious interest, intent, and dedication in the Department as a point of contact for those many issues where really serious attention needed to be paid to getting things done. You have just been a wonderfully helpful partner in that regard. I'm going to miss the chance to interact in those ways but hopefully find other ways to do so.

I think we should all recognize that Secretary Leavitt has really elevated the importance of these issues and this Committee into a place that it needed to be and was gradually finding its way into that kind of visibility, but this has really come into its own because of his strong leadership and his interest in personalized medicine.

That has been wonderful to see happening. I certainly remember those years going back, because there are a lot of them, where it was really hard to get that kind of traction. People didn't necessarily appreciate that this was a topic or a set of topics that were in need of that kind of high level attention. It has been wonderful to see that happening.

I see Greg Downing standing in the back. I also want to give a real shout out to Greg here for the way in which he has played such a critical role in the Department in terms of being a leader in trying to wrestle through these many interconnecting issues that have needed that kind of high level attention and that he has done so well.

Steve, I thank you for your kind remarks and your willingness to step into the role here of leading this enterprise and to do so so effectively. Your predecessor Reed, of course, played that role so effectively.

The work is not done. Clearly, as you all wrestled with the agenda items yesterday, there are many things that need attention in a pressing way. The American public really needs all of you to be able to be sure that we take this remarkable moment in history -- and it really is -- where we have the opportunity to transform the practice of medicine and make sure that we do so in a fashion that benefits people and doesn't expose them to unnecessary risks.

That means moving all of these disciplines and

all these issues together in a way that really only a group such as this can effectively do.

It has been a great honor and a great privilege to be the NIH liaison to this group. I'm going to miss that. I may take up your invitation and sit in one of those back chairs in the future meetings because I will not stop my interest in personalized medicine.

In fact, one of the things I hope to do during this unemployment phase is to write a little book about personalized medicine because I think there is a lot of interest in the public and perhaps a need for that kind of a depiction of what we know and what we don't know in a fashion that is accessible to people who don't have Ph.D.s in genetics. Maybe I could make some contribution in that regard.

I don't know where I will land. I don't know where I will be a year from now. That is part of the adventure, is to try to figure that out.

But, thank you, all of you, especially Rick and Steve, but all of you for the wonderful friendships I have been able to make, the colleagues I have enjoyed working with over these years, and the accomplishments

that together we have managed to do. It has been pretty amazing, pretty breath-taking. There is much more to come. Thank you all so much.

[Applause.]

DR. TEUTSCH: Thank you so much, Francis. Thanks, Rick.

Let me turn this session over to Sylvia Mann Au, who is going to lead the discussion and continue the discussion on personalized genome services.

SESSION ON PERSONAL GENOME SERVICES

Overview of Session and Introductions

Sylvia Mann Au, M.S. CGC

MS. AU: Yesterday the Committee had the opportunity to participate in Secretary Leavitt's Personalized Healthcare Initiative Workshop that explored consumer interest in understanding of personal genome services offered directly to consumers.

This morning, we have the opportunity to continue the discussion of the personal genome services by looking at the broader landscape and including the state of the science and the public policy considerations of these types of services. We will also have the chance

to look at another angle on the consumer interest in these services.

Following the presentations by the invited speakers, the Committee will have a chance to discuss what our next steps might be in this area, specifically what SACGHS might do to do further study of the implications of personal genome services.

If you look in your briefing book under Tab 4, you will find that our wonderful and capable staff have prepared summaries of the talks and background information in there, which I have found very useful, especially the summaries of each of the companies for later on.

This morning we are fortunate to have Dr. Teri Manolio come and speak to us about the state of the science behind personal genome services. She is the director of the Office of Population Genomics of the National Human Genome Research Institute and senior advisor to the director of the NHGRI for population genomics. Wow, that is a big title. She has had this position since 2005.

Dr. Manolio is also professor of medicine at

the Uniformed Services University of Health Sciences. She will be providing us an introductory overview of the current state of the genomic research with a particular focus on genome-wide association studies.

Dr. Manolio will have 20 minutes to present to us, and then we will have 10 minutes following her presentation for questions and answers. Thank you, Dr. Manolio.

The Science of Genomic Associations: Current Status and Future Directions

Teri Manolio, M.D., Ph.D.

[PowerPoint presentation.]

DR. MANOLIO: Sure. Thank you very much. Good morning to you. You can see in your briefing books the questions that I was asked to address. This could probably take a week or so to go through.

[Laughter.]

DR. MANOLIO: I have but 20 minutes, so I will do my best.

This is an interesting time to be discussing this. I think we all recognize that as of, maybe, four or five years ago the genome was a pretty barren place

when it came to associations with complex diseases. There were maybe a couple of associations that were known, actually through linkage studies. But it really wasn't until 2005 when this first finding on age-related macular degeneration was found by genome-wide association. In 2006 there were three more associations added, and then things really began to pick up. It has really been remarkable in the past year, 2007, and even into this year, to the point where we can barely get everything all on the same slide.

This has caused, in 2007, the general science to dub that year the Year of Genome-Wide Association Studies. This was the breakthrough of the year in human genetic variation.

This was based on, primarily, the HapMap, first building on the Human Genome Project and the sequence of the genome, and then the development of a haplotype map that basically showed the relationship between the various 10 million single nucleotide polymorphisms, or SNPs, the most common form of variation to date in the human genome, and the relationships among those so that one doesn't need to measure all 10 million of them but

you can measure a smaller subset and then use that to infer relationships across the genome. The second generation map was just published last year.

The goals for the HapMap were to use just the density of SNPs needed to find associations between SNPs and disease, not to miss chromosomal regions with disease associations, and basically to make a tool to assist in finding genes, and really, what a tool it has been. Then, recognizing that one would need more SNPs for more complete coverage of populations such as those of recent African ancestry who have shorter stretches of linkages to equilibrium.

In parallel with the development of the HapMap, and in large part probably stimulated by it, the cost of genotyping has fallen dramatically. Shown here in this slide from my colleague Steven Chanock, in 2001 we thought we were getting a very good deal if we paid about $1 for a single genotype.

Those costs fell dramatically as the number of genotypes per test increased. In 2005 we were getting this for about a penny a genotype. Costs have continued to fall. This now is almost a two-year-old slide, and

these costs now are at about the $400 range for about a million SNPs in a single individual. So, truly a remarkable reduction in cost.

This has led to a huge host, as I showed you on that previous slide, of diseases and traits that have had genome-wide associations done. As of last night there were 58. I haven't checked this morning, but there are probably another couple because they come out very, very rapidly.

This onslaught of information has been referred to as "drinking from the fire hose," from David Hunter and Peter Kraft, who observed that there have been few, if any, similar bursts of discovery in the history of medical research. I think we can all agree with this. This has really been an incredible time to be in genomics.

We have been trying to keep up with this at the Genome Institute. We have a genome-wide association catalog that is put together by my colleagues Lucia Hendorf and Heather Junkins. I look over their shoulders at times. You can find this on the genome website or you can just Google "GWAS catalog" and it should pop right

up. This provides information on the study, the diseases under study, the number of people examined, the region of association, the gene, the odds ratios, P values, minor allele frequency, as much information as we can pull from these papers. This is just about a full-time job for two people to be able to keep up with this. It is really quite something.

But we would refer you to this if you are interested in knowing what are the most up-to-date findings. We are a little bit behind in keeping it updated.

In looking at this with the associations through about May, we were looking particularly at the SNPs that have been identified in terms of what they actually are or what they do in the genome. One would have expected, prior to about 2001, that most of these would have been in coding regions in the genome. In fact, there were big debates about one should only do the HapMap in the coding regions or one should only be sequencing in the coding regions.

In fact, the variance that one would have expected to be the most powerful in associations, those

that change the amino acid that is used in putting together a protein, or that cause the protein to be truncated entirely, only 13, or about 6 percent, of these 284 were actually in those regions.

Another three of them were what are called synonymous SNPs, where there is no change in the amino acid but there may be a change in the speed with which that protein chain is produced.

Then, maybe about 40 percent of them [were] in the introns and not in particular splice regions where the exons are stuck together, but in the intronic regions of no known role.

Then, a few [are] in the untranslated regions of the messenger RNA, a few more in the five-prime promoter region of the genes and then the three-prime region that also may play a role in the speed of translation. Then, nearly half of them [are] in other or unknown regions. This, I think, has been one of the big surprises of this.

So, lessons learned from these initial studies. Genes that wouldn't have been on anybody's candidate gene list are now popping up for these diseases. Macular

degeneration everyone thought was an ischemic disease. It is actually very strongly related to complement factor H, an inflammatory disease-related factor. Coronary disease with a cell cycle variant, actually previously related to melanoma. Childhood asthma, type II diabetes with a cell cycle gene, QT interval prolongation with nitric oxide synthase.

Prostate cancer has been shown to be in what is called a "gene desert." Finding after finding after finding, beginning with the Decode Group, showing associations in this region where there aren't any genes at all. Also, in Crohn's disease, a similar kind of thing, with multiple regions without known genes.

Then, signals in common across diseases. You might have thought that these two were similar, but boy, CHD and diabetes don't have a lot in common with melanoma and they all share this strong association. All these forms of breast cancer, Crohn's disease, and psoriasis are related to each other, but Crohn's disease and type I diabetes are not, and yet they share a strong association. At least they were not known to be. Rheumatoid arthritis and type I. So there are lots of

surprises in here, and many more surprises to come.

In addressing the first question, what are the recent advances and how have these facilitated the emergence of personal genomic services, probably the low-cost, high-throughput genotyping is now within reach of large-scale population research studies. That has then generated all these incredible findings.

Over 150, probably more like 170 now, such studies are completed, with over 180 well replicated loci in nearly 60 diseases and traits. So, in just three years, really an unbelievable bounty of findings.

Genotyping costs are now also within the reach of at least perhaps well-to-do consumers. That has been a considerable change and one that we would not have seen just a few years ago.

Things that I don't have time to talk about but are on the horizon and you should keep on your radar screens are associations with copy number variants; next generation sequencing, which you will hear a little bit about, I suspect; the Thousand Genomes Project, an international project involving the NIH and many other groups to identify even rarer sequence variants and

alleles that might be associated with disease.

Then, DNA methylation, epigenetic changes, catalogs of gene expression. All of these are things that probably will provide even more valuable information about genetic associations.

The second question I was asked to address is for which diseases are strong genetic associations and/or markers established. I guess I would turn back to you and say define "strong." One could have a lot of debates about what metric one should use. Is it a large odds ratio, so people who carry the risk allele have a five-fold increased risk of disease than people who don't carry it, or a two-fold, or a 20-fold.

Is it a very small P value. The association that you observe is very, very, very unlikely to have occurred by chance because, remember, we are testing millions of SNPs in many, many, many studies. So, is that a good metric.

Is it a risk allele that is very common. Instead of being 5 percent of the population or 10 percent, is it in 80 percent or 90 percent, as some of these variants are.

Is a large proportion of the disease attributable to the risk allele. There are ways of estimating this based on the prevalence of the risk allele and the odds ratio, the population attributable risk. There are certain assumptions that go into that that really don't apply to genome-wide case control studies. I won't go into it further, but you will see that metric used.

Or, do they explain a large proportion of the genetic variance and therefore would be expected to play a large role in the disease.

Let's look at a few of these metrics, again from the catalog. Here are the odds ratios that have been detected for a variety of variants, just a number of associations. You see that the vast majority of them are below about an odds ratio of 1.3 to 1.4. The only reason this drops off here is that the power to detect these loci is very low. One needs very, very large sample sizes. Probably, this is a distribution that goes up through the ceiling at these low ranges.

But there are a few that are much larger than this and one or two that are considerably greater than

that. Maybe those are ones that you would want to focus on.

Similarly, for P values, I have plotted here the negative log-10 of the P value. Here is the number of associations, here at 10-to-the-minus 10th. Most of them are at this level because 10-to-the-minus 7th is about what is generally used for genome-wide significance. But there are some that are less unlikely than that, even out to 10-to-the-minus 80 or 10-to-the-minus 100. Are those much more believable? Probably. They might be ones that you would want to focus on.

How about the frequency of the risk allele. You can see there is quite a range of these. Most of them cluster around the 30 to 40 or 20 to 40 percent range. Some of them are much rarer, but some are much more common. Some are associated with fairly large odds ratios. These, again, might be risk variants that would be particularly important to focus on.

I was asked for which diseases are there lots of genetic associations shown. Crohn's disease has probably been the big winner. This paper from Barrett, et al. in last week's Nature Genetics showed 32 Crohn's

disease loci. Many of them do not have associated genes with them. You can get this from the paper much better than from my drawing, but it makes a visual impact.

In that paper they also show the proportion of variants explained, another metric that one could use. You can see that, again, the vast majority of these loci explain 0.1 to 0.2 percent of all of the genetic variability that one can estimate from family studies. That is not very much. There are a few that explain a little bit more, but you will also notice that this drops off a fair amount.

This dotted line is the power to detect risk loci. You will notice that it drops off quite steeply below about 0.1 percent of the variance explained. So, as we are able to detect more of the variance we probably will find more of the variants, with a T.

What those mean at the very low proportion of variance explained is, again, another matter for debate and may be very important in terms of identifying pathways or mechanisms or druggable targets, et cetera.

Next, I was asked what criteria should be used to determine whether associations between a marker and a

phenotype is strong enough for the marker to be included in genetic testing. Here again we have that "strong enough" that I was stumbling over previously.

Because we are in the District, perhaps like a politician I will say I don't like this question. I would rather answer a question that I would pose.

[Laughter.]

DR. MANOLIO: What criteria should be considered in determining whether a particular variant should be included in genetic testing. Then, also like a politician, I won't answer it but say that it depends to a very large degree on the purpose of the testing.

So, what would the purposes of genetic testing be. You will say, silly thing, of course what we want to do is improve health and prevent disease, but how best to do that. One could provide targeted, proven risk reduction strategies to those identified to be at greatest risk. We currently do this with non-genetic factors. It makes sense to do it with genetics.

We could identify persons at high risk for later rapid implementation of newly proven interventions. This is being done in eye disease. We don't yet have

interventions for these diseases, but wouldn't it be wonderful if you had these people already identified and could just pull them in and start giving them whatever intervention was necessary as soon as you had proven it.

To improve the cost efficiency of non-genetic risk reduction strategies. So, other ways of reducing risk may be targeted in people at higher genetic risk.

Possibly to facilitate reproductive choices, or even to provide information that may be of personal value to individuals regardless of whether we might consider that to be actionable or valid or useful. People can make their own choices, and that may be an appropriate reason as well.

I'm sure many people around this table could provide much better criteria than I could, but just to throw some things out for you in terms of things to consider, obviously here we are at strength again. But, whatever the strength of the evidence is for an association with risk.

Availability and acceptability of proven risk reduction interventions. If you don't have a way of reducing this risk, one can debate how valuable it is to

identify it, although there are those who would argue it still is useful.

The validity, availability, and cost of the test. The potential anxiety, stigma, cost, additional testing, or other harms from receiving the results to an individual. The confusion that it may give to their physician, et cetera.

Trade-offs in other testing or care that cannot be paid for within a fixed budget. So if we paid for this kind of testing or this kind of targeted work, we may not be able to pay for something else.

This was explored in great depth in a recent paper by Paul Feero, et al., from the U.K., where they do have, clearly, a fixed budget for health care, in the recent New England Journal. [It shows] what they estimated to be the distribution of genetic risk in the U.K. population for breast cancer using only seven known loci related to breast cancer, which explains, actually, less than 10 percent of disease. But that is not bad when it comes to these complex diseases.

What they estimated was taking those seven genes, you have two alleles at each locus. Basically,

you could have 2,200 different combinations of genotypes of those three genotypes in each of those seven loci.

You could look at women who have none of the risk alleles at any of those seven loci, and they would be at this lower end of the distribution of risk. For those who don't think in logs, this is a relative risk of 0.4. So, in the U.K., the risk of breast cancer for women at age 50 within 10 years is about 23 per thousand women. For these women, it would be 40 percent of that, or about 10 or 9 per thousand women. There are only about 60 such women per 10 million in the U.K. population. This is somewhat population-specific because of allele frequency differences.

At the other end of the distribution, if you had the risk alleles for all seven, two copies of the risk allele at all seven loci, you would have a relative risk of about 2.5, which means that instead of a 23 per thousand risk you would be at about a 60 per thousand risk, which is a considerable increase. Only about seven to 10 women would be in this group according to these estimates.

What is shown here is a nice estimate. This

heavy black line is based on the current loci. One could identify 50 percent in the highest risk group. So, here is the proportion of the population based on genetic risk. It would include about 60 percent of the cases. Down here at 20 percent of the highest risk would include about 28 percent of the cases. So you have almost enriched your population by about 50 percent.

Interestingly, they project if you were able to identify all of the genetic loci that were associated with disease, you actually in the top 50 percent would have 88 percent of the cases. In the top 20 percent you would have 64 percent of the cases, a three-fold enrichment. So you could really do quite well in terms of targeting screening.

Then, how could one improve the efficiency of these screening strategies. A 50-year-old woman in the U.K., as I said, has a 2.3 percent risk, or 23 in 1,000, of breast cancer in the next 10 years. Currently, the U.K. recommendations are to offer mammography to all women over 50 each year.

One could say perhaps one should offer screening to all women at that particular risk level and

possibly not to offer screening to women who are not at that risk level.

Women in the 40th percentile of current risk, just based on those seven loci, have a 10-year risk at age 50 of 2.1 percent. Now, this risk is somewhat age-dependent. So, maybe you don't want to test them at age 50. You might want to wait until age 60 or age 55, or whatever.

This one is not all that different, though, from 2.3, so you might not get excited about that. But how about the women in the 5th percentile population risk. They have a 10-year risk of 1.5 percent, and they actually never reach a 2.3 percent risk because they die from other things they are at such low risk. At least these are all estimates, and the kind of estimates that one could expect to see.

This, again, is based on only seven loci. Would one not offer mammography to these women? Again, a difficult decision to make but one that we should be considering if what we are talking about is targeted screening.

Lastly, what are the limitations in risk

assessment for disease. Most markers, I think as you have heard repeatedly, are not deterministic. Many people who don't have the markers will develop the disease, and many people who do have the markers will not develop the disease.

Much of the genetic risk remains unexplained. At best, we are getting about 10 percent of the variance explained in many of these complex diseases. In many diseases we are not even close to that.

Plus, there is little or no evidence to date that interventions based on genotype will actually improve outcome. We need that kind of evidence.

Genetic markers may, though, provide additional risk information so that you could target more aggressive risk management and carriers of those variants. But again, there is little evidence to support this.

Some have likened this kind of risk information to a cholesterol level. They carry about the same risk, 1.3 to 1.5 in some cases. One would never not measure a cholesterol level even if you knew many other risk factors. It is something that would be, perhaps, equally useful to do with genetics.

Remember that cholesterol is quite different. There is a huge body of evidence of the effectiveness of cholesterol lowering in preventing heart disease. In just a smattering of the recent papers plus the most recent, the third adult treatment panel, the consensus panel in the U.S. and many consensus panels abroad, this evidence took 30 to 40 years to put together. Do we want to wait that long to develop that kind of evidence for genetic variance. Probably not. Do we want to bypass this step entirely. Also, probably not.

So, what kind of research is needed. There is lots. I think we will be talking much more about that today. This is just one example. It is cited on page 8 of your brief. The multiplex initiative from my colleagues at NHGRI, Collene McBride and Larry Brody, is designed to test a number of risk variants, about 15 or so, for common complex diseases in basically healthy people and then provide that risk information back to these folks and see what changes they make in their lifestyle, their health behaviors, et cetera, and also to create an infrastructure to facilitate this kind of research.

I realize that you are probably used to researchers coming to you and saying what we need is more research, and that does seem a little self-serving. Indeed it is. But we have to recognize we are very early in this technology. Like this early microscope, it is a mammoth. We have a fair amount to do before we learn how to refine these techniques and to apply them so that we can improve health and prevent disease. Thank you.

[Applause.]

Question-and-Answer Session

MS. AU: Thank you, Dr. Manolio. Do we have questions from the Committee? Julio.

DR. LICINIO: I have a question. I think this type of work is extremely important of course, and I think coming up with new candidates is fundamental. One thing that people often forget is that in the issue of cholesterol lowering the drugs were discovered through work in very specific families that were very rare. From those rare genetic findings you can generate the most commonly used drugs in all of medicine that apply to everybody, mostly people who don't have the genetic problem. So I think discovering new targets is crucial.

But I think what people out there don't understand very much, and I wonder how we can improve that, is the concept of risk. If you have a 2 percent higher or lower risk of having diabetes or having higher weight or whatever, you could have that genetic component and not have the risk at all. If you have a 1 percent chance of dying as a result of something, you could be the one in 100 and die or you could be one of the 99. This gives a prediction.

It is very hard to communicate that to people and for people to understand it. We had another meeting yesterday that I'm sure you are all aware of. Someone came from the audience. The person got tested in one of these consumer-based genetic companies and was told that she had a very low risk of colon cancer, but her father had colon cancer, she had the polyps, and she went on to take care of herself and look at that very closely as opposed to just ignoring it.

So you could have a 1 percent risk of developing something and you could develop it, and you could have a 99 percent risk of developing something and be that one person that doesn't have it. How does that

get transmitted to patients, to doctors, and to the healthcare system.

DR. MANOLIO: I don't have a good answer for that. I'm a cardiovascular epidemiologist. We were just thrilled in the Framingham Study when we came up with a risk score that would tell people that you are not just at the usual 0.5 or 1 percent risk of disease, you are at 10 percent risk of disease, we need to do something about that. People would say, "Well, that is only one in 10. Heck, what does that mean?"

There are others around the table that I think can probably comment on that better than I.

DR. KHOURY: I wanted to ask a question, and this a very clear expose, I guess, of the field of genetic associations and the GWAS era right now. Thank you for your comments.

I want to make one comment and then ask a question. I think what I heard you say is that the low P values we are seeing and the low odds ratios are not necessarily translating into clinical validation yet because we have predictive values, probabilistic information, increase your risk and decrease by a certain

amount.

More importantly, I think I heard you say something about clinical utility. If you take the example of cholesterol, which took years in the making before widespread population screening was adopted, I think you said do we want to wait that long? Perhaps not. But, do we want to implement right away? Perhaps not. So, where is that balance? That is the first question.

The second one is, in your estimation where does the field of genetic association and its clinical utility lie compared to more traditional ways of stratifying risks such as using traditional risk factors and/or family history.

I can cite you data from [the] cardiovascular [field.] In the State of Utah, people like Roger Williams many years ago found that 15 percent of the families in Utah cluster about 50 percent of all cases of heart attacks in the whole State of Utah based on their genealogies, and they didn't do any genetic testing. It was only based on a family history score.

So, what is the value added of genes vis-a-vis

pure family history and other existing risk factors that we know of today?

DR. MANOLIO: That is a critical question, Muin. Nobody really has looked at that very well. There have been a couple of estimates in diabetes that I'm aware of looking at the proportion of disease that is explained by genes. At that time only two or three were known. It may be a 58 percent area under a receiver-operator curve, which you are familiar with. Basically, 50 percent is dead even. You don't do much better than chance. Fifty-eight percent is not all that much better than that. If you use things like age, sex, BMI, and family history, you get it up to 88 percent, and no genetic information at all.

Family history for Crohn's disease. If you have a first-year relative with Crohn's disease you are at a 25- to 30-fold increased risk. Do you need genetic testing if you have a family history of that. Perhaps not. On the other hand, as the example of cholesterol illustrated, the LDL receptor variants that were identified in people with familial hypercholesterolemia are in less than 1 percent of the population.

If you did a genome-wide association study, you probably wouldn't even see that, or it would be at the 1.05 level. But in certain people those are very high-risk alleles and they lead to a pathway or a mechanism that then works for everybody, except, ironically, in the people who are homozygous for that defect, when the drugs don't work at all.

So there are trade-offs here that one has to make. But I agree; the research really needs to be done to prove that this information adds to what we currently know.

MS. AU: Paul.

DR. BILLINGS: Thank you. I thought that was very interesting. I wanted to pick up on one line of argument that you raised, and it is colored by my experience during my training over the battles at establishing mammographic standards for screening of women.

So, as I understand your argument, it is conceivable that there would be a recommendation not to provide mammographic screening for a subset of women who might have none of the risk alleles that were identified.

What kind of study would have to be done to undo what is a blanket and relatively well evidence-based standard of mammographic screening that is now recommended for all women above the age of 50, let's say?

DR. MANOLIO: No, it is an interesting question and a very challenging one. Probably, the only way really to nail that would be a randomized trial, where you screen some women and you don't screen others based on their genetic variants. That would be a very large trial, and it would take a long time to conduct.

Could one do this from observational data. Probably not in the U.S. because mammography still is not universally applied. It is something that goes along with a whole host of other health behaviors. There may be other places where mammography really is universally applied. In the military, possibly, or in other controlled populations in the U.K. or Canada or other places where the healthcare system is really much more organized and standardized. Those might be places to do it. But, really, probably a randomized trial is what would convince most people.

Please understand, I'm not advocating that we

not screen people based on their genetic risk. I'm just saying that that is one possible conclusion you could draw.

MS. AU: Any other questions? Francis.

DR. COLLINS: Just one comment in terms of the state of the art at the present time. Teri has nicely summarized what this deluge of discovery has offered us in the last couple of years, which is enormously exciting in terms of the insight it provides in terms of pathways involved in disease that we really didn't suspect, with most of these loci being completely unexpected in terms of exactly what their function is. It opens up entirely new directions in terms of therapeutics, which is a wonderful aspect of all of this.

But in terms of the heritability, as Teri has said, we actually are not yet in the position of being able to identify more than a small percentage of the heritability even for a disease where we have several loci identified. When you add it all up, there is still a huge missing heritability factor in there. There is much debate about exactly where is all the rest of that.

Is it going to turn out that those are rare

alleles of large effect which you would not find by a genome-wide association study but you would find by sequencing. Much effort is going into applying sequencing for just that purpose.

Are these copy number variants, which are not particularly well assayed by the SNP chips that most people are using. These are, of course, large segments of DNA that may include entire genes or even whole sets of genes that are present in more or fewer copies depending upon your particular inherited version of that copy number variant. You can imagine that could have pretty interesting effects. People are rigorously now trying to look at that, although the technology is still tricky, to be able to say you have scanned the whole genome for those things.

Have we missed on some kind of gene-gene interaction so that individual effects don't look that impressive but if you actually had enough power you would be able to see that when you have a combination of a certain set of risk alleles it is not just additive. Things actually go substantially higher. So far, really not much evidence for the people that have looked at it

to show that.

But I think it is fair to predict that in the next couple of years this whole question of where the rest of the heritability is, is going to get pushed pretty hard. As this Committee is deliberating about where this is going, you should expect that that percent that is accountable is going to go up. It is going to go up to a degree whereas, in the very nice example of the Feero, et al. study in the New England Journal, you are going to start to see that curve rising up more and more in the direction of being able to make more and more predictions about the place where the risk is most apparent.

This is obviously a bit of an unpredictable trajectory scientifically, but I think it is fair to say that is the direction we are. Whatever plans people are thinking about making in terms of the application of this to public health are going to have to be integrated with the sense that this is a moving target and that there is a lot more information just around the corner.

We are just starting down a path that is likely to have all kinds of interesting twists and turns and put

us, potentially, in a few more years, in a more powerful position to make those predictions than the rather weak evidence that we have right now with these small odds ratios only adding up to a few percent of the heritability. That is going to change.

DR. TEUTSCH: I think our last question goes to Mike.

DR. AMOS: Teri, thank you very much for that. I think it is really important to get beyond the press and get to the real science of the issues.

Steve and I were at a conference last year at the Mayo Clinic where you gave part of this presentation. You have added a lot to it. I don't mean to put you on the spot, but somebody asked you the question, is it even worth doing whole genome analysis studies anymore. You said you guys were thinking about that a little bit.

Where is your thinking now, and where does it fit into the context of the broader research? I see this as a part of the complete disease signature. History, physical, and all those things come into play, but also many other biochemical and anatomical parameters.

DR. MANOLIO: Sure. Genome-wide association is

all the rage, but it really is today's technology. Probably, tomorrow's technology is whole-genome sequencing, and that is really coming within reach, as you will hear from some of the later speakers.

My personal prediction, and there are others who share this view, is that genome-wide association will probably not be the tool of choice for research and discovery in the next few years, maybe five or so, maybe a little bit longer than that. In whole genome sequencing one gets the entire genome. Now one has to figure out how to analyze the entire genome, and we are not quite there yet.

But it may be of great value in terms of assessing an individual's risk not just for one disease but for, maybe, a hundred diseases. If you look at multiple diseases across an entire individual, you are probably going to find each of us is going to be at risk for at least one, probably three or five. We may be at very high risk for those diseases. Wouldn't you like to know that. You can probably capture that with a genome-wide association study without doing whole genome sequencing.

But, as Francis pointed out, things are changing very, very rapidly. We will just have to see where it goes.

MS. AU: Thank you, Dr. Manolio. Our next speaker is David Ewing Duncan, and Mr. Duncan is the director of the Center for Life Science Policy and visiting researcher at the Graduate School of Journalism at the University of California at Berkeley. He is an award-winning, best-selling author of six books and numerous essays, articles, and short stories, and a television, radio, and film producer and correspondent.

Mr. Duncan is also the founder and editorial director of the Bioagenda Institute, which is an independent, nonprofit program of events and educational initiatives that discusses and analyzes critical issues in life sciences.

Mr. Duncan will be presenting his perspective and experience in utilizing multiple personal genome services. Mr. Duncan will be presenting for about 20 minutes, and then the Committee will have about 10 minutes for questions and answers again.

Thank you, Mr. Duncan.

Personal Genomic Information: A Consumer's Perspective

David Ewing Duncan

[PowerPoint presentation.]

MR. DUNCAN: I want to thank the Committee for inviting me. Good morning. I did want to say briefly, after the parade here thanking Francis Collins for his service for many years and as a journalist, Francis is always accessible. He has always been very clear in explaining things. We always deeply appreciate that. So, thank you very much, Francis, for all of that over the years, the journey that you and I have both had and that you have had with other journalists.

I have a lot to cover here in 20 minutes. I'm here this morning as one consumer, a party of one, a subset of one, who has been tested by all of the major genomic testing services that have been discussed in these meetings and actually quite a bit more.

I'm not your average consumer, I have to hastily add. I am a journalist covering biotechnology and an author that is writing a book called Experimental Man: What One Man's Body Reveals about His Future, Your Health, and Our Toxic World. That was my publisher's

subtitle. You can tell me what you think after my presentation.

For the book I'm having not only my genes tested but also environmental impacts on my body along with tests on my brain, organs, blood cells, microbes, proteomes, and other assorted -omes. I will add here that this is all non-invasive, which is part of the point of these tests.

I'm also the director of a new program at the University of California at Berkeley called the Center for Life Science Policy, as was mentioned. We are launching this fall, and there will be a lot more information about this coming out over the next few months, for those who are interested.

In conjunction with my book, the Center for Life Science Policy is developing the Experimental Man Project, which is an educational effort that includes a website and other activities.

The experiment, by the way, that I'm running is for one man to take and analyze a wide array of new tests that aim to forecast the future health outcomes of a healthy individual. This is a rather radical concept

which I will talk about here and there in the presentation.

I started this project with a visit to my physician, who declared me to be a healthy white male, 50 years old. I always love that medical terminology. Occasionally one's name is mentioned in there when they are describing you.

I also come from a mostly healthy family that lives a long time, some of us actually over 90 years old, a couple even over 100. So we don't have a lot of heritable diseases floating around that are obvious, anyway.

As we enter this brave new world of personalized medicine, I want to emphasize what we are talking about. This has been mentioned over and over again, but it is worth mentioning again in a consumer context. In the past we have focused on the ill and the unhealthy mostly, since pretty much the beginning of human history. We face a future here that is a focus on the healthy individual, which is quite exciting, on prevention and improving health. Essentially, we are trying to predict the future in a way that hasn't been

done before.

The Committee has asked me to address several questions, which are listed here. I'm going to summarize those in groups in the presentation here, the first one being expectations. "What were your reasons for pursuing personal genome services?"

I have already mentioned my primary purpose was really as a communicator and a journalist. I also have a natural curiosity about technology and information. I keep wondering if there will be a Pandora gene discovered one of these days, which I certainly am homozygote high risk for.

A distant third, really, for me anyway, was an insight to my future health. Coming from a healthy family and considering myself pretty much "impervious to disease," that was a distant third.

"What sort of information did you anticipate receiving from these services?" I actually had fairly low expectations of getting extremely useful information. The normal consumer I'm not sure would certainly have the access and information that I have as a journalist, so that is partly colored by the fact that I knew going

into this that this is an early phase of the science.

I also probably deep down, when I really think about it, wanted confirmation that I am as well as I think I am. Yesterday we had a presentation from the Yankovich group about different categories of patients. I'm not sure exactly where I fit in, but I'm probably the one that likes to keep myself healthy and doesn't do it because I think I might get sick but because I like to be healthy. I don't think much about being sick, thankfully.

Also, I went into this with some expectations about what my family results might be. That was a different set of expectations because I was asking other people, members of my family, who were also tested, by the way -- my parents, my brother, and my daughter -- on some of these tests. It did make me pause a minute bringing my family into my experiment, but they very heartily agreed to go along with this.

The next set of questions are tests and results. This is going to be the bulk of the talk here. "What tests did you take? What were your results? Were there differences, overlapping results, et cetera?"

A baseline of the tests that I have taken. I have been tested on most of the major SNP array chips, some insertion/deletion information, some copy variants. I have also been tested for several dozen individual genes and coming in the next few months I'm hoping, anyway, to get my full genome sequence. We are working on that right now. By the way, that is plenty of information even without the full genome, as you will see here. Trying to figure out what exactly one makes of the full genome is another question.

I have been tested by many companies and academic labs, nonprofits. I was one of the few people around 2001, which is of course the jurassic age for genomic testing, that actually had several hundred markers tested for a Wired story that I wrote back in 2001. That was even before Craig Venter announced that he had been tested by his own company. So, very early on getting some results.

I do want to emphasize that some of these results and this information has been around for a while, so although we have been having this flurry of association studies coming out this information and its

attempted application on individuals and consumers has been around for a while.

The costs of all of my tests. If you add up all of these numbers, my individual test was around $16,000. If you add my family in, it is about $20,000. I'm gratified that many of the companies and labs did this pro bono or some of the costs were covered by publications that I was writing for.

By the way, if I get my full genome sequence, it will be quite a bit more money, at least $100,000, perhaps much more.

Participants. As I mentioned, my mother and father, who are both in their mid 70s and very healthy; my brother, who is 48; and my daughter, who is 19, is a biology major at St. Andrews in Scotland and basically made me test her. I was a little reluctant to bring my daughter into this. She is over the minority age. It was her decision and she insisted, and there we have it.

I'm going to focus on three companies primarily that have been discussed a lot, what they call the Big Three, although I think DNA Direct should also be on there as maybe the Big Four. You will hear details about

these companies and can read about them in the packet that was given. From a consumer point of view, there are two or three differences in each of the companies that are worth noting.

Navigenics focuses primarily on diseases. They do not do ancestry or some other traits of that sort. They do offer counseling, and they are more expensive than the other two sites, at $2,500.

These images, by the way, are my results. You can't really see them in detail, but you will get to see them in a minute.

deCODEme offers a few more diseases. They also have ancestry and other attributes. deCODE we have to say, too, is also a publicly traded company. It has been around for over a decade. They do drug discovery. Their scientists have come up with at least some of the major studies that all of the sites use in the association studies. So they have some scientists actually working in their back shop as well as having a website.

At the moment they offer no counseling, and they come in at $1,000 or so.

23andMe is also at $1,000. 23andMe hits the

jackpot for the larger number of traits that they feature. It is interesting that they have a rating system that they put into their large number of traits. They rate these traits whether they are preliminary or established. While there has been some criticism of that rating system, how accurate it might be, I think that is heading in the right direction for consumers to try to understand which of these traits has the best science behind it.

Two other approaches I want to mention just quickly here, one of which you will hear from later. DNA Direct, which is one of the older online companies, offers only individual tests, primarily for those who have a predisposition in the family or some other reason for ordering a test.

I have had one test ordered from DNA Direct, and it was a different experience than the others because they do have a heavy counseling aspect to this. I talked to the counselor two or three times. Also, they have an extraordinarily rich site of information which includes pros and cons of testing. It actually tells you reasons why you shouldn't take the test as well as why you might

want to take them.

The Coriell Institute is not represented here, although I would recommend that the Committee look into what the Coriell Institute is doing. There is a small blurb in the materials I was given about them. Their genome-wide testing website will be up in the next few months.

This is a nonprofit. I'm sure you all who are scientists know of them for producing tissues and storing cell lines. They are going to be testing for free on a Navigenics-style test with 15, 16, 17 diseases, about 10,000 to 100,000 people over the next several years. They have NIH funding and other grant money.

They are also doing something interesting for those who consider doctors to be less educated than perhaps they should for genetics. They are starting out by testing doctors in the Philadelphia area, where they are.

Now to the results. I'm going to give you results for three diseases for the three sites that I mentioned. The first two were rather randomly chosen: age-related macular degeneration, because it is an A and

was at the top of the list on some of the sites. Being, as I said, a healthy person, I don't have many anecdotes or stories to tell about how this affected me because I came out, actually, pretty well on most of these.

But if you look over to the right-hand columns, and if you have a minute you can study this chart more thoroughly. I don't have time to go into all of the columns here. But the critical numbers and items for a consumer would be the ones in color there. This is a threat level color code, much like you would get in an airport, which I have added here just for convenience sake.

You can see in that age-related macular degeneration for the individual SNP risk factors that I have threat level colors that range from green, which are quite low risk, to red, which are high risk. The second-to-last column there on the right tells you which company gave me the result for which SNP.

By the way, there are a number of different SNPs here, as you notice, for the same disease. Different SNPs for the different sites as well.

On the far right are my lifetime or overall

risk factors that the sites give. They list several SNPs, different risk factors for the SNPs, and then an overall risk factor.

The far right is the average risk, and this is interesting for a consumer, and a bit head-scratching. The average risk for the different sites are different. My risk factors are also a bit different. In this case it is not a huge factor. I am low on all of them, which is really all I want to know, but it is worth noting that there is a bit of difference there among the results.

Another way to present the data here for diabetes type II, comparing the three sites. There are 19 different SNPs that I counted when I went online on these three sites a few days ago. They are changing a lot, so who knows, they may have changed by now. But, 19 different SNPs among the three sites for 15 different genes.

My range of results were yellow, 0.82, to 2.61, red. That was the only red, actually, out of the 19. My lifetime risks for the three sites were within shouting distance of each other, about 4 percent apart, which isn't bad.

The average of all the sites was around 25 percent for type II diabetes. I'm below that, which is also, as a consumer, really all I want to know. So that was good news.

It is worth noting that there were only four SNPs that overlapped on all three sites. Out of those four, two of them actually had different enough results that they raised an eyebrow for me, meaning that the same SNPs had different risk factors associated with them on at least two of the sites.

There are four additional SNPs that were on two out of the three sites. So there were overlaps of an additional four on two out of three. Then, 11 orphans that were just on one site only.

Is the data consistent. Basically, to summarize this slide, I would say within acceptable parameters for at least this consumer most of it was fairly consistent. The one area that was a little strange was to have all this variance of risk factors within a disease, all the way from green to red. In talking to the companies, they all correlate those and use them as modifiers to come up with that final score,

but that is a little confusing to present such widely diverse results for people that don't really comprehend or understand how one would factor all that into a final score.

There was one exception, however, and that is my heart attack gene markers. I don't have heart disease in the family, but I did get what I considered somewhat confusing results for my heart attack gene markers on the three sites. On one site I have low risk, on one high, and one might say in the middle. For something like heart attack, this is probably not the most comforting results. Actually, for someone like me who wants to confirm that I'm healthy, it is not going to be useful information to have such variance in results.

Again, you can see my color-coding there, the range from yellow to orange to red. On the far right are these lifetime or overall risks. For deCODEme and Navigenics you have a spread from 42 percent decode risk factor for me, to 62 percent. The average is 49 percent, according to the sites. 23andMe uses a slightly different method, although it is worth noting that my risk factor is almost twice the average on the 23andMe

site, although I think I noticed when I went on last night that that risk factor had slightly changed.

Why the different results. I do encourage you to, obviously, talk to the companies about this. But some of the information that I have gleaned as a reporter, and you can obviously see it even as a consumer, is that there are different SNPs and studies used, as I intimated, for the different diseases. There are different methods for determining risk for the different websites. You also have different methods for determining combined SNPs, as I have mentioned.

There is also a reliance on correlative SNPs, which I don't really have time to get into. That has to do with linkage disequilibrium and the fact that not everyone in a population actually shares correlative SNPs. In other words, sometimes you are homozygote, sometimes you are heterozygote, is my understanding of this.

Again, I am not a scientist. I should have said that at the top of this. These reflections are through a person who is trying to comprehend and understand this, and I hope I get it right but this is

how it has been explained to me.

In the end, this heart attack result did leave me scratching my head, wondering what it all meant. I did, with later tests in the Experimental Man Project, find out that I did hit the mother load in a Mendelian sense of a lot of high-risk homozygote SNPs that indicate that I do have a higher than normal risk factor for heart disease. I will get into that in a second.

[As to] the three generation study with my family, I will just go over one result which was a bit surprising. We did find out that my father and my brother were heterozygote for Alzheimer's. I was sitting there one morning in San Francisco as the sun was coming up over the bay and turned on my computer and got these results back. That was a little disconcerting because, as a non-scientist, to see anything to do with Alzheimer's is a bit scary. We don't have that in my family, but I called a couple of experts right away. They reassured me that, actually, the heterozygote risk for this is fairly low. Homozygote is what you don't want.

I called my father, who is 76 years old, about

to turn 77, and he shrugged and said, "Well, I have made it this far. I'm probably okay."

My brother, who is 48, equally shrugged. We come from Puritan stock from the Midwest and we just don't talk about these things very much. But he seemed to be unconcerned and hopefully that will continue.

I want to mention very quickly here the difference between a rare disease and a common disease for a consumer or for a patient. My brother does have a rare genetic disorder, which is osteogenesis imperfecta. It would have been fantastic to have had a test to know this early in his life. We went through a lot of turmoil within the family trying to figure this out.

I'm not sure, however, and I discussed this with my family, if we would want to find this out in a direct-to-consumer sort of process. It may be in the future that one doesn't even think about that, that is how you get the information. At the moment, my brother, anyway, would prefer to get this through a medical professional.

The sites at the moment that we are talking about don't offer rare diseases, probably for this

reason. But it is worth thinking about.

Recreational and preliminary. I won't spend a lot of time here. Ancestry is fun. I encourage it for everybody. I don't have bitter taste. I seem to have a lower IQ by three points. I am at a substantially higher risk for heroin addiction, and I am going to live to be over 100 despite my substantially higher risk for heroin addiction.

[Laughter.]

MR. DUNCAN: The crush of data which has been mentioned by Teri and others is something also to think about here. We are talking about a very small number, although it seems like a large number because it has come so fast, of association studies.

From my Experimental Man Project, we are up in the upper hundreds now of markers, and many of these are for rare diseases and things that I would have no business really looking into normally but I'm trying to do everything for the Experimental Man Project. If I printed out my Excel chart at the moment, it would be about 24 feet long, and it is going to get much longer.

The final step here, or the final list of

questions, are reactions and thoughts. "Did you alter your behavior in light of test results? If so, how?" I want to emphasize again that I am atypical here, both as a journalist and also having much deeper knowledge because I have been tested on many sites.

But the answer is that I did not really alter my behavior. I did have some subsequent tests, as I mentioned, which are not yet ready for consumers, algorithms by companies that do huge modeling which they factored in many, many things. I did find out that I have a higher risk than normal for heart attack and I did alter my diet. There was some talk about statins, but I have not indulged in that yet.

Breast cancer data. I was going to talk more about that, but I will discuss that with people later. We did have that show up on some of our results as well, which was some concern for my daughter.

The pluses of direct-to-consumer testing. One gets a great insight into personal and societal health with accurate results. You get a certain personal empowerment. I believe that the appearance of these companies and these websites is actually pushing along

this process much faster than it was going. It is pushing the health industry and the health research establishment to think more about applying this great research, which much money has been spent on and much effort, towards individuals and establishing guidelines and ethics education and funding.

I think we need more of this. This is a fabulous discussion to have here, driven really in part by the appearance of these services.

Opening up new avenues for research and medical and drug development, which has been mentioned.

A few minuses at the moment, and most of these I consider to be somewhat temporary, but important. This is early days. Association studies are not always applicable to individuals. That was actually not the original intent, is my understanding of much of that science.

Disease and non-disease results are sometimes mixed on these sites, which at first is somewhat jarring, although I guess you get used to it after a while.

There are no standards that I can tell as a consumer that reassure me of the validity of these tests,

and especially the risk factors. The number at the end of the day that you want as a consumer is that number. What is my risk factor.

I think consumers are perhaps a bit smarter than sometimes they are given credit for. I think if you explain to them over and over and over again even the fact that these risk factors may change over time as the information becomes more available, people will begin to understand that and pick it up. There needs to be an educational process for that.

A minus is that most physicians, including my own, who is a wonderful physician, really had no idea what to do with the information when I brought it to him.

There is a potential to frighten certain people. I don't think we are hitting that market yet with these early adopters, but we certainly will. Then, the high costs and who is going to pay.

A few thoughts and suggestions. Consumers, I believe, should be free to access their information and buy services, and in fact they will. Any attempt to harness this information or keep it away from consumers, especially with the Web the way it is, being amorphous

around the world, people who want this information will be able to get it in some way.

I love the discussion that is going on here and would encourage that as a consumer to help me and others understand.

Early adopters I think should be part of the experiment. Again, I suggest looking into the Coriell approach, especially the fact that they are testing doctors first.

We need to establish guidelines and standards, I believe, for the tests and the information, uniform risk assessments, et cetera. Kind of a Good Housekeeping Seal of Approval, if you remember that. I think most consumers would like to have some kind of assurance that this information is accurate. In fact, that was reflected in one of the studies that was commented on yesterday.

Also, who will pay. And a few others here. I think it would be helpful to have a crash program to set validation standards. This is clinical validation standards in preventive medicine.

Disease markers I believe are more important

and should be handled differently than, say, ancestry.

I believe that physicians should be involved with some of the decisions in the companies in assessing people's results.

Also, 23andMe recently did start offering a locator system online for finding a genetic counselor in your area. We could possibly do that for physicians as well. This is fairly easy with the technology and computers today.

To conclude, I want to go back to the beginning. Genetics is just the beginning of this process. In my book and in the Experimental Man Project, we are also doing environment, brain, and body. I have a funny feeling that a committee like this, or this Committee, will be in session for many years discussing each of these new developments when we start applying envirogenetics, as we call it, and environment-gene interaction.

There is a lot of interesting research going on with using brain waves, for instance, as biomarkers. FMRI studies, as you all know, are very small and in the early days right now, but they will begin to play a role

in preventive medicine, et cetera.

I would love to have you all check out our new Experimental Man website, experimentalman.com. We are just getting it going, but this will eventually download all of my results. We will have a wiki-style site where others can participate in what we are calling the Experimental Man Portal, where various groups, companies, and others who offer information about applying genetics to individuals will be able to have a link from the site.

Finally, the book comes out in March. I hope you all will pick up a copy. Thank you very much.

[Applause.]

Question-and-Answer Session

MS. AU: Thank you, Mr. Duncan. Now we will take questions. Muin.

DR. KHOURY: Thank you so much. This is fascinating; one person's journey into the genome. Just a couple of comments and then I will ask you to tell this Committee what it should do, because this is an advisory committee to the federal government. Some of your closing slides were about people should access this information but there should be guidelines and

information, the seal of approval so to speak. And, who will pay.

So there are these mutually exclusive categories. If we get an independent group to evaluate these technologies, then they return [saying] "Don't use them until more studies are done," that could be one recommendation from one group. At the same time, consumers are free to do whatever they want with them.

You went in with your eyes open as to the potential limitations of this technology which is early on. But if you are advocating for guidelines and information, how do you reconcile the need for guidelines with the individual freedom to seek whatever you want. Maybe those two things are not as mutually exclusive as much as they are in my mind.

If somebody tells you, "David, this stuff is nonsense right now," you would have still gone and gotten it, wouldn't you. You were not going in for the medical application. You were going mostly for the curiosity and the recreational aspect and essentially to validate what you already know, that you come from a healthy family. So that cardiovascular signal was a bit disconcerting.

Anyway, I'm throwing too much stuff at you. I would love to hear what you have to say.

MR. DUNCAN: First of all, I really did this as a journalist and a communicator. It is important. When I first did the Wired story back in 2001, we almost didn't do it because it just seemed like a reporting gimmick. But I learned from that and also a story I did for National Geographic a couple years ago where I had several hundred environmental toxin levels inside of me tested. This is a fabulous way to communicate science using a real person as an example.

I said right off that I'm a bit different than most consumers, but I suppose it is all driven by a certain curiosity.

In terms of the contradiction you mentioned, or the potential contradiction, I'm really talking about, in a pragmatic way, it is not that hard to go out and get this information on yourself. You can get it tested in any number of ways.

What you end up getting is what I have, several disks with a lot of lines of data, with results that don't tell you much. But there are already cropping up

online a SNPedia, this website which has been mentioned. I have talked to the guys that run that, a couple of young researchers, and one of them I believe is down at Emory. They can run it through what they call a Prometheus Program. I have not been able to do that because I have a Mac and it is only on PC at the moment, but they will run, free of charge. It is fairly crude, certainly, compared to the online companies we are discussing. But there are ways to do this, in other words.

So it may seem like a bit of a contradiction, but I'm being more just a pragmatist here. This data and information is getting more accessible, and there are ways to analyze it independent of anything we are talking about here, any guidelines that might be established perhaps.

But I have thought a lot about who might establish these guidelines, and this is where I'm putting on my new hat at the Center for Life Science Policy at Berkeley and beginning to think in terms of policy. I think one has to balance very carefully the fact that this is a new technology. Silicon Valley in San

Francisco, that is where I live. We see these things come frequently. It is important to let these new technologies find their wings and how they are going to work.

It is important that the commercial sites came online here because I think it is tweaking everyone to think about this in a way that they didn't before.

There may be a way to make this voluntary. I think there is some discussion among the companies. It may be that the government at some level needs to step in. I think these are things for you all to decide, in discussion with the companies.

At the end of the day, though, as a consumer, I think one needs to have some sense, and again, that was borne out in one of the surveys yesterday. In fact, I believe it was said that accuracy is more important at this point than even the issue of privacy, which I haven't discussed at all here. Obviously, I'm releasing my results to the world, so it is not as important to me, the privacy issue. I may be completely an idiot for doing that, but we will find out.

But I think the accuracy issue is going to be

very important in a Consumer Reports sense. It may be that there are independent groups. There is a lot of discussion even at our center and some other areas [like] academic institutions for creating ratings systems.

I think this will all naturally occur very quickly. This Committee could collect information on that. It could be very useful to have input from all of you and some guidance in figuring out how that process would happen. But I hope that answers the question.

MS. AU: Scott is next. Could I ask the Committee to keep the questions short so we can get back on time?

COL. McLEAN: Two short questions. [That was a] really fantastic presentation. Was it your plan to share your information with your personal physician from the beginning? The follow-on question is, what experts did you consult and how did you find them?

MR. DUNCAN: I started out the whole process, even in 2001, with my personal physician. My personal physician for the original project has retired, but these were very knowledgeable people at UCSF. My current physician is the head of ambulatory medicine there and

has more knowledge than most people, although when I brought in some of these results he had to go online and look up some information before he was able to really tell me much. When I start bringing in things like brain scans, he really starts rolling his eyes.

I'm sorry. What was the second question?

COL. McLEAN: You found some consultants, some experts to help guide you when you got specific results. How did you find them and what qualifications did they have to give you feedback on what you had come up with?

MR. DUNCAN: As a journalist reporting on biotechnology for some major media outlets, I have access as a journalist. That is mainly how I was able to access people. Basically, my job is to go out and try to find people like Francis and others who can comment on these things. I take that very seriously. I have so much material it is piled high in my office.

But I also try to get a balance of opinions on this as well, which is really important because there are, obviously, a lot of different opinions and stakeholders and others that need to be brought into the equation. Much of that will be in my book.

MS. AU: We have Paul Miller next.

DR. MILLER: This is very interesting. Thank you. I was struck by what I perceived to be an underlying assumption that I heard in your remarks and actually heard yesterday also. That is about the term "health" and the search for I am in good health and I am seeking good health, as if we know or maybe people have agreed on what is good health that everybody is seeking, and that these technologies are offering insight into.

I was thinking about this question of health against the backdrop of two things raised by genetics that I have learned from Francis. Human variation is a natural part of the human experience. So we have anomalies that are a natural part of human experience. Yet we have these technologies and these companies that are offering the search for genetic anomalies to identify difference with the expectation of exactly what? To eliminate difference? To create better health?

I have achondroplasia. People have deafness. Yet I consider myself in good health, but yet I have a genetic anomaly.

So I'm curious from your perspective how you

see that, if you have thought about some of those questions in your journey.

I'm particularly struck by your brother who has OI, osteogenic imperfecta. Had you had a conversation with him or your parents, had they known that 40 years ago, would they have done a gene screen to potentially look for an embryo with OI and then eliminate it? Is your brother in good health or in bad health?

MR. DUNCAN: He is not in fabulous health, but this disease has made him disabled and he is no longer able to work. It would have been nice to have known, I think, probably more for the family than him.

I pursued this trying to figure out what exactly was going on with him through contacts and work with Peter Bayers, who is a prominent geneticist at the University of Washington and an expert on osteogenesis imperfecta. He actually sequenced both my genes involved and also my brother's, COLA1A and COLA2A? 1A? Francis can set us straight on this. They make collagen.

So I pursued this. My brother, interestingly enough, on the conference call when I was up in Seattle with Peter Bayers, said it is all very interesting, what

he has, but at the moment there is no real effective treatment for what he has. He is taking some of the drugs that slow down bone loss. But he wants a treatment, and Dr. Bayers immediately said that is what we are after here and that is why we are doing these tests.

I think that is a case where it would have helped our family dynamic to have known this, certainly, because we didn't really know what was going on with him and we were frightened by that. We didn't really even recognize it as being a problem because we come from such a healthy family.

But it is interesting you said the word what is "healthy." Throughout these conversations, including yesterday, as a writer and a person that works with words, I think many of these words we need to back up a minute and even define. I'm not really sure. I know that I feel healthy. I know it when I see it, which has been applied to some other things, too.

But validity, the word "valid," what does that mean? I thought a couple times of raising my hand yesterday in the discussion. People throw [words]

around. What is a valid marker. What is clinical validation. That is the word "valid." The other one is "usefulness." I think I understand that one a little bit better, but [I am] a writer and a word person.

We keep talking about Francis here. Sorry to keep putting you on the spot. But, maybe since he has become a wordsmith as well, we will get some more information on that.

But I think it is important that we define these words in a way that everyone can understand them, including the public.

DR. MILLER: I think it is interesting that you keep on defining your family as a healthy family, not withstanding your brother's OI and other issues. So I think health is generally relative. What is a concern is what are these technologies doing to relative assumptions about health and unhealth and how is that related to disability and non-disability.

MR. DUNCAN: There is a philosophical component here, too. I do keep saying that because that has been my mantra my whole life. I'm one of these people that even at 50 years old still considers myself somewhat

invincible. I'm beginning to realize that is not the case. I put that out there because we all have different ways of viewing our health. I think it is interesting.

My brother's situation, he was very healthy until a certain point. I still have to stop and pinch myself and remember that he is not now, and that is a real anomaly for my family. So you are catching me up here a little bit on very deep-felt sensibilities about who we are, or who I am.

MS. AU: We have Paul Billings, Joseph, Mike, Jim, and Mara, and we are going to cut it off there.

DR. BILLINGS: David, thank you very much. I have a three-pronged question for you.

MR. DUNCAN: Do I need to get my pencil out, Paul?

DR. BILLINGS: No, no, it is okay. These should be straightforward.

As an experimental consumer as well as an experimental man, what is your perception of the error rate of the laboratories that you were engaged with? Do you think it is low, very low, never occurs? What is your perception?

MR. DUNCAN: There are various levels of potential accuracy or errors here. I think anyone that knows these tests that are run in the CLIA-approved labs tend to be very accurate. I have been run more than once on most of these chips and actually did an analysis, at least on a lumina chip, on two of my results on the same chip and it came out with almost no error rate. So that end of the spectrum is, I think, very accurate.

I did have that slide. We are going to be doing a more quantitative analysis of the various sites, not only the three here but any others that come within our purview. So I don't have the data on that, but just my swag feeling is that, as I said, I think there is a parameter in most of the results that were fairly consistent. Accurate, that is another one of those terms we may have to define here.

We need to remember, from a consumer point of view anyway, and any other point of view, these are moving targets here as more information comes in. This is something that is really important, I think, to emphasize to consumers and the public. This information is only what we know now and it will continue to change.

Even the sites as I have been monitoring them over the last several months, they changes. Different SNPs come on. My risk factors move around a little bit. New features are added.

Again, I don't think consumers will be overly bothered by this as long as it is explained properly.

DR. BILLINGS: The second part of my question is, for those traits that you have increased risk, how will you monitor them and what evidence are you using for your style of monitoring?

MR. DUNCAN: Well, I don't really have that many. I am monitoring the heart situation. I would love to share with you the fascinating tests that I have had that actually did convince me with a high degree of accuracy that I do need to watch myself and that, funny enough, with a huge algorithm that I was tested on, a couple of the genes that are cited on the sites that we are discussing actually did have an enormous impact on steering this entire algorithm.

I had carotid ultrasounds, a CT scan on my heart, lots of chemistry, and lots of other genetic tests, and a couple of these association study SNPs,

especially those on Chromosome 9, did have an enormous impact. We even ran the algorithm as if I was heterozygote instead of homozygote high risk and it did affect the curve quite a bit.

I would be happy to share that with you. That is coming down the pike not too long from now. Actually, the company involved there can offer this test for under $1,000 and it will probably be out within a couple years.

DR. BILLINGS: Then, lastly, are you intending to disclose the results of this test when you apply for life insurance?

MR. DUNCAN: I contacted my insurance company. I think Ryan Phelan said that yesterday, too, or someone, that they had tried to share this with their insurance company. I haven't gotten much of a response. The insurance industry seems to be sitting back and trying to analyze and figure all this out.

I did speak to the major national actuarial group about a month ago and asked them about this. They said at the moment that these association studies don't yet have the predictive power than an actuary really would need to apply them. But I think one can see that

there is going to be enormous change.

I'm extremely lucky. I have low risk factors for most of these disorders. If I'm looking around and saying who should pay what, I no longer have the same risk factors as everyone else in this room. In fact, everyone has a different risk factor. On a shared risk sort of system for insurance, how do you determine that if we all know we have different risks? So I think that is a challenge that will be coming up for how we go forward with insuring ourselves.

MS. AU: We still have Joseph, Mike, Jim, and Mara. Can we keep them to single questions, please?

MR. DUNCAN: I will give a quick answer, too. Sorry.

DR. TELFAIR: Just as you get to me. Okay.

[Laughter.]

DR. TELFAIR: Thank you for the presentation. I appreciate that. My question actually is just interrelated. I want to switch the questioning a bit.

In terms of where we sit as a Committee, our real concern is what it is that we can recommend for the population as a whole, a public health question. So I'm

asking you a public health question. In terms of use of the information, what is your expected outcome for use of what it is that you are doing in terms of beyond this, and whether you have one or not.

The other part of the question is, what would you recommend related to prevention? I noticed that the argument yesterday for a number of the DTC panel was that there is a lot of added value to knowing in terms of motivating behavior. We know that that is really not the case in so many cases, and you yourself just confirmed it wasn't.

So in terms of use for the information and in terms of what recommendations would you make to the population in terms of prevention and that sort of deal.

MR. DUNCAN: Again, I think we are in an interim phase here and things are in great flux. In the future what I believe will happen here is that we will have batteries of tests. This is already beginning with some neonatal tests at the very beginning of life for some people. We will continue to have expanded batteries of tests earlier and earlier in life that will give us some indication.

I sometimes pull out my iPhone, which I think I have here somewhere, and I believe sometime in the future, maybe the next generation, we will have something called, maybe, an iHealth that will actually tell us and give us probabilities and possibly even measure things like what is in the environment around us and other measurements like that that will be factored in and do all the work for us and tell us what is coming up.

I don't know about living in that world. It would be interesting. Some people will embrace that. Some people will be perhaps frightened by it.

But I think when you are talking about predicting the future, which is essentially what we are doing here, we are a long way from really doing that for most people. The rarer the disorder, obviously, as you all know, the more predictive power there is.

But in terms of guidelines for preventive care, I mentioned a few of my thoughts and ideas. I think we need to accelerate dramatically this process to validate, whatever that word means, but to clinically validate, to spend some of the resources we have been spending on the pure science now and shift over rapidly to applying this

information to individuals to find out what is really going on.

If one comes out with a homozygote high risk for prostate cancer, which was mentioned yesterday, I think what a consumer wants to know, and to make it really effective, would be to do a thousand of those, or whatever the number needs to be in a clinical test, and get a biopsy. You actually come up with some results that are meaningful.

So I'm hoping that the federal government and others who have the resources to apply to this will focus more on the individual now and how this science applies to the individual. Does that answer your question? Sort of?

DR. TELFAIR: It is okay. I can't ask another one.

[Laughter.]

MS. AU: You can beat up Mike and get his question.

[Laughter.]

DR. AMOS: You can have my question. I'm going to hold it. I'm going to talk about standards and

standardization a little bit later. But you have my question.

DR. TELFAIR: I appreciate that, but I think I'm going to save it for the DTC panel.

MS. AU: So then we will move to Jim.

DR. EVANS: It was a really fascinating presentation. You are doing something right because you look far younger than 50.

I'm interested in this idea of personal empowerment because it came up yesterday as one of the justifications for doing this and doing it now. My feeling, and I want to get your take on it, is that personal empowerment only follows from the prior demonstration that this is useful information. There is a large percentage of people in this country who find their horoscope personally empowering, but I don't think. that we should really be in the business of encouraging personal empowerment based on illusory ideas of what is really useful.

So, does it make sense to you to separate out this idea? Right now, getting your genotype at 500,000 sites, do you think that is personally empowering or do

you think that needs to wait until we actually have some evidence that you can do something with it before it is truly personally empowering?

MR. DUNCAN: I think my story is that it has not been particularly personally empowering given what you said. In fact, and this was one of the possible outcomes of this experiment, most of it has not been particularly useful for an individual. In fact, most of it was not designed to be particularly useful for an individual, which is a primary point here.

I'm talking more about the future and I think what people would like this to be. Any information that a patient or a consumer who is interested in their health can have and understand and use on their own I think is important. There is, of course, an extremely important role for care givers, physicians, and others.

In this age when consumers have so much access to information, there are those, as we heard yesterday, that seek it out, that are almost desperate to have it, I think it is incumbent on this Committee and others in positions of responsibility to figure out a way to create an atmosphere where people feel that these are accurate

without squelching or throwing the baby out with the bath water.

As I mentioned earlier, there is an ongoing experiment here on how to apply this information, which is very useful and actually quite exciting. These three or four sites here that I mentioned all have different methods. If you throw in the Coriell Institute, you have a nonprofit model there. I know of several others that are out there about to start.

It is one of those delicate moments where in this transitional phase I think responsible parties need to make sure that there are some accuracy and guidelines as much as possible and an educational process to explain to people this is a transition period, alongside allowing these experiments to go forward in a responsible way.

MS. AU: The honor of the last question goes to Mara.

MS. ASPINALL: Thank you, but I'm going to keep it to a simple question. The role of genetic counseling. You spoke about that on a couple of sites and throughout the initial part of your odyssey. What was the role of counseling? How did that make you feel more and less

comfortable, and how do you see that playing out in the future?

MR. DUNCAN: I think at this phase people are not used to getting results online. Some are. Again, I'm in the Silicon Valley culture. People are much more used to receiving information. It is always interesting to come back to Washington, where I lived for a long time and worked, and the East Coast. We are much more involved with getting our information perhaps online back in the San Francisco area and on the West Coast.

But I liked having the option, first of all, as a journalist, of being able to talk to a bunch of people and understand these things. But I did go through the process as a consumer would with those sites that offer genetic counseling. Of course that was reassuring.

I was getting these services pro bono. I don't know if I would be willing to pay thousands of dollars for that. I might have to think about the price points on that. That might affect my answer.

But I think having some access to somebody that you can talk to if you need to [is important], and that is why I mentioned in my thoughts and ideas, having given

this some careful thought, that maybe one way to deal with this is to have physicians that review these results possibly hired by the companies or maybe independent, I'm not sure which. But, somebody watching to make sure that there isn't something a consumer misses.

I think that is important. There may be some result there that they don't really fully understand that is important medically. I think there needs to be some system for that.

It would be great if all the sites would have genetic counselors you could call and talk to. I don't know if that fits into some of the business plans. Perhaps it should.

MS. AU: I would like to thank Mr. Duncan. In the spirit of trying to catch up with some of our time, can we try to make it back here by 10? We will take a break right now.

MR. DUNCAN: Thank you very much.

[Applause.]

[Break.]

MS. AU: We are going to continue the session on personal genome services. The next session is a

roundtable with the five companies. Each of the companies will present for approximately 10 minutes, less if you can do it, and then we will have a question-and-answer period after everyone has presented.

Just like the NFL, we are going to give them a two-minute warning before the end of their talk, with no timeouts. A two-minute warning with no timeouts.

Our first speaker is from Navigenics, Dietrich Stephan. He is the co-founder and chief science officer at Navigenics. Prior to his current role, he was the deputy director of discovery research at the Translational Genomics Research Institute and still holds a faculty appointment there.

Through his research Dr. Stephan has identified genes and contributed to the understanding of genetic predisposition for multiple diseases.

Thank you for being here, Dr. Stephan.

Personal Genome Service Providers

Presentation by Dietrich Stephan, Ph.D.

Navigenics

[PowerPoint presentation.]

DR. STEPHAN: Thank you very much for the invitation. It is really a pleasure and an honor to be here today. While we are getting the slides up, I would also like to congratulate Dr. Collins on the first half of his career. Well done.

[Laughter.]

DR. STEPHAN: While we are getting geared up again, I thought it might be useful to remind you that all human disease has a genetic component. I think we tend to forget that sometimes. On the one side, we have monogenic disease, where a broken gene causes the disease. There is no environmental component.

On the other side of the spectrum we have trauma, if you will, or infectious disease. But even those have genetic drivers with respect to healing and interactions with a pathogen.

The original vision of Navigenics was to, early in life, completely articulate your entire germ line genetic risk for all human diseases and then, across your life span, unmask portions of that information that may

be useful within that window of life and then use that information in conjunction with a physician to either avoid environmental stimuli that might kick off that complex genetic disease and put that person on a focused biomarker monitoring program.

You could envision a serum biomarker for cancer at its earliest stages that you could ascertain if you knew an individual was genetically loaded. Ultimately, [you could] either put someone on a primary prevention therapy or treat the disease early so that you could reduce the burden of disease for that individual but also do that on a public health level.

I should mention I was trained in a public health department. I also trained with genetic counselors for the first two years of my career. So I come from a monogenic testing background. What I would like to do in these 10 minutes is perhaps convince you that what we are talking about today is not so different from what we have been doing for the last 20 years in the field of medical genetics.

For the first 15 years of my career I was involved in doing linkage analysis to identify broken

genes that definitively cause disease. We have been successful in doing that. We have identified the genetic basis of about a dozen monogenic diseases. Those were really easy to find homes for, meaning you could toss a mutation across the fence to a molecular genetics testing facility and have it adopted. We had medical geneticists who knew how to interpret that information. You have the mutation and the loss of function mutation with a penetrance metric associated with it, and this is what is going to happen to you, your unborn child, or your planned children.

We have that entire infrastructure, but we didn't at one time. We didn't have that infrastructure. There were no genetic counselors at one time, and it is recent history.

Now that we are doing medical resequencing of genes in people who are unaffected, we are starting to understand that penetrance in itself is a concept that is going to be modified dramatically moving forward. As we start doing whole genome resequencing in unaffected individuals, we are going to be turning up people that are compound heterozygotes for mutations that don't have

a phenotype. What does that mean in the context of traditional medical genetics and genetic counseling. That field that we understand as set in stone is evolving as well.

What I would like to posit is that alleles of "low effect size," of odds ratios between one and 10, are not so different than monogenic mutations with penetrance variables associated with them.

But before I get into that, I would like to, over the course of the next, I guess, eight minutes, communicate to you that we are facing a healthcare crisis in this generation. We don't want to underestimate that because I believe that that should be the primary motivator for all of us. We are on the trajectory; I think everyone would agree. The key driver of mitigating that crisis is going to be prevention, I believe. If you believe that, then we should use all of our pre-symptomatic risk information to maximize our ability to focus our prevention efforts and improve outcomes across the population.

"Genetic risk factors" is a term that I really like because it embeds all of our understanding of

environmental risk factors into what we are going to be talking about today. They are not so different, genetic risk factors and environmental risk factors.

These genetic risk factors can be used to refine risk in a clinical setting in addition to other types of risk factors. We need a new delivery vehicle for these types of genetic risk factors. You can look at someone and say they are obese or they smoke. You can't look at someone and say they harbor a 9P risk variant, and you can't place that type of genetic testing into the traditional monogenic testing environment because it is not geared to do that.

We have done a lot of monogenic disease identification, and here are a couple of examples. We have also, in my group, identified the alleles that drive several dozen common complex genetic disorders. This was a paper we published in Science. It was the first paper that used over 500,000 SNPs to paint the genome and identify chunks of the genome that co-segregated with disease or were enriched in people with diseases versus without diseases. We went on to continue to flesh out the Alzheimer's story with another allele that seems to

be withstanding replication by the community.

We do this also on a national level. I chair an NIH-funded consortium. This is funded by 15 NIH institutes. It provides these types of genome scanning and interpretive analyses for the entire scientific community, essentially. We have done over 400 projects. Many of those are whole genome association studies.

The point here is that we come from an understanding of the technical nuances from which this information is derived.

I just couldn't stomach going out and raising another $1- or $2 million to do another one of these whole genome association studies without an implementation infrastructure waiting on the back end. It seemed like a frivolous exercise to me.

Now, don't get me wrong. On the therapeutic side this is incredibly useful information. But on the risk assessment side there was no infrastructure. So I have taken a sabbatical from TGen to found Navigenics, along with David Agus, to understand how we can use this hard-wired risk information to alter the natural course of common chronic diseases so that we don't see these

explosive rises that are anticipated. This happens to be Alzheimer's disease, but this same curve can be drawn for any of the common chronic age-related diseases.

Really, the only way to alter the course of this massive trajectory, looking at millions of people costing the healthcare system trillions of dollars, is through early detection and preventive strategies. This vision came about that I already articulated where we get a genomic sample early in life, we fully sequence the genome for both common and rare variants, and de novo variants, do holistic copy number analysis, sift through all of the epigenetic modifications and sequence the mitochondrial genome, and push all of that information together.

Remember, we are building the infrastructure to do this. The interpretation doesn't exist yet for the vast majority of these.

[Then we would] put all of that into a big computer and push a button and get a rank-ordered list of your predispositions that you can then practice preventive medicine around.

Now, for a few common complex conditions the

information does exist and is robust. I would posit for, for example, disorders like age-related macular degeneration, hemochromatosis, Alzheimer's disease, we have captured a significant amount of the genetic contribution and continue to do this.

But we recognized we are building a new industry, so from the very outset we understood that there were ethical concerns, there were counseling learnings that hadn't been done yet, clinical paradigm shifts, et cetera. So we really, from the very beginning, from the inception of this company over two years ago, built a gold standard team, from the board of directors to our clinical advisory board, really understanding how does medicine need to evolve or change, or should it, and how do we interface with the medical community in the appropriate way.

The scientific advisory board, folks like David Botstein, Isaac Kohane, Nick Schork, and others, are really trying to guide us through this complex science to really understand how to provide genetic counseling. This can be very important information to an individual. So we have, for example, the past two presidents of the

National Society for Genetic Counselors on our taskforce.

Then, of course, policy and ethics. An important component of that is Paul Slovic, who is a risk communication expert. So, do you communicate risk as 1 percent or one over a hundred. How do you use colors. How do you use words to maximize the accuracy of the risk information that you are providing to someone.

We have also taken great pains to build a team of genetic epidemiologists in-house -- so, genetic epidemiologists and epidemiologists -- to vet all of the literature that comes down the pike with respect to I'm going to call this validity.

These are [what] we are calling our curation criteria, but we believe that these are more practical curation criteria than, for example, the Venice criteria because, without a loss of accuracy of significance, they allow us to really click through studies and identify what is real and what is not by fully reading those and then implementing those on our risk assessment panel.

From day one we have decided quality is of the utmost concern. I should mention that for the first year and a half of the company's existence all we did was try

and understand the regulatory environment. We probably spent over $10 million just trying to understand how we would click into the established environment. We feel like we have really digested and understood how to do that.

This is an example of that. From day one we decided we needed a CLIA-certified laboratory with extremely stringent QC and QA parameters. We are measuring quality on a per-SNP basis across the population with respect to Hardy-Weinberg, equilibrium checks, et cetera.

Also, we have put a lot of effort into understanding how we use retrospective case control data -- given that this is a germ line constitutive insult, if you will -- to go from odds ratios to relative risks. We have muddled this out and we feel like we can do this fairly accurately. I can point you to our website where all of our information is fully transparent.

You have seen some of this this morning as well, but given the current common risk variants that we have, how much predictive power do we have. What you see are a bunch of ROC curves. These are all generated by

downloading the primary data from Framingham and Wellcome Trust and other data sources and actually applying our algorithms onto those data sets to understand the AUCs and ROCs. These are also going to be available.

I would like to segue now into talking about, just briefly, a common argument, that these genetic effect sizes are so low you shouldn't bother with them. The genetic effect sizes that we are talking about -- odds ratios or relative risks of between one and five, let's say -- are exactly on the same scale and order of magnitude of the environmental risk factors that our public health community has commonly messaged.

The next argument is, these haven't been studied enough. If you look at some of these papers that have been published, for example the 9P variant that predisposes to myocardial infarction, that has been studied in close to 17,000 people. That is a fairly large data set. It has been replicated twice, again in data sets of a thousand individuals each.

So I would say the numbers here are often on par with environmental risk factor studies. But what you see here in black are homozygote odds ratios for the

genetic risk factors that Navigenics is testing for. In gray you see the heterozygote risk effect sizes. The triangles indicate the environmental risk factors that we have culled from the literature as being valid for the common diseases we are testing. You see there are all in the range of between one and 10.

A practical example and then I will end. This is the state of the art of clinical reassessment for myocardial infarction that is practiced in the primary physician's office. The physician will test your blood pressure, probably do a cholesterol test, and ask you if you smoke, if you exercise, or if you have type II diabetes. Based on this information, generally if you have three of these things, you go on a statin and you are told "You better be careful or you are going to have a heart attack."

Very rarely are these things plugged into the Framingham Risk Calculator. In the real world, if you have two of these you are probably going to get a heart attack. Here is a statin. If you have one of these, go home and watch yourself and be good.

But these are the effect sizes that we are

talking about that are driving clinical decision-making. Now if you add in the two vetted genetic associations, you see that the effect sizes are exactly on par with this. So to say we are not going to use that information because it has the word "genetics" in it, or we are not going to use that information because there is nothing you can do about the genetic variant, I don't quite buy that argument because there are lots of things you could avoid to balance out your genetic load.

We have decided we need professional access to counselors and physicians. The whole reason we went DTC in the first place was a conscious decision so that we would minimize the possibility of health insurance and life insurance discrimination. Now that we have gotten GINA we are relaxing that a little bit and building out our physician channel. You will see a lot of that moving forward.

But basically, we are trying to use genetic information to motivate behavior change, and there is evidence of this being published. For example, the Reveal study shows minimal distress to people who got their E4 results. This is a wonderful study by Aspenwal,

et al, that was just published that shows people who are at high risk for melanoma based on a family history then got genetic testing. Those who got genetic testing went and got screened more often than those who just had a positive family history, showing that the word "genetic" can motivate behavior change.

I will end with this slide saying that Navigenics doesn't make tools, we don't decide on what to do in the clinic after a person gets their screen done, but we believe we can digest all of the information that is in the literature accurately and provide that in a transparent and accurate way to an individual so that they can use that risk information moving forward.

I should say we will be turning on monogenic testing very shortly for hundreds of genes and the capability to capture rare variants and common variants for common disease moving forward, which hopefully will explain more of the heritability that Dr. Collins talked about.

We have ongoing clinic trials with the Mayo Clinic, for example, to understand how this information changes an individual's outlook and how best to

communicate it, as well as with Boston University and Bob Greene there. So, thank you very much.

MS. AU: Thank you, Dr. Stephan.

[Applause.]

MS. AU: Our next speaker is co-founder of 23andMe, Linda Avey. Prior to 23andMe, she developed translational research collaborations with academic and pharmaceutical partners for Affymetrix and Perlagen Sciences. She also spent time at Spotfire, helping scientists understand the power of data, visualization, and applied biosystems during the early days of the Human Genome Project.

Welcome, Ms. Avey.

I would like to remind the Committee members that there is information about the companies in Tab 4 of your briefing book.

Presentation by Linda Avey

23andMe

[PowerPoint presentation.]

MS. AVEY: Thank you, everyone. It is really great to be here in person. I think last time I was on the phone. It is always better to be in person. I think we are going to have some problems here with Adobe Acrobat, but we will try to get through this.

As you all heard, especially from David's wonderful presentation -- that was really fantastic -- we are really on the very forefront of a journey that I think a lot of us are going to take together. That is why I'm so encouraged to see all of you here today, willing to really have a conversation with us as we embark on this experiment, really. That is really the way we look at this.

23andMe is really a new way to do what we hope will be a very effective tool in research: the ability to really engage with consumers for the first time in a very large-scale and Web-based way to conduct genetics research.

What we embarked upon with 23andMe last November was to enable individuals to get access to their genomes really for the first time in a very broad way. What we see ourselves as a company doing is providing an

interface to that genome. What we like to do is tell people that this is really the early stages. We have been doing these genome studies now just for a very brief time really, when you look at the history of research and the discovery of the DNA molecule, all the way through the great work that Francis and others did in sequencing that wonderful molecule, now being able to give people access to it and give them dynamic tools and ways to really interact with that information we think will really move and change the field of how we are going to conduct research.

What we have done is we have this system now where you can order our service through sending in a saliva sample. We extract the DNA out of that. We work with a CLIA facility. Then we generate this set of about 600,000 data points for you.

As Teri Manolio so beautifully pointed out -- I would love to have that slide where she has all the chromosomes and all the papers -- 2008 really has been a watershed year in GWAS. Having come from Affymetrix and Perlagen and seeing all of these wonderful tools that companies like they and Illumina have created, we are

really now see the fruits of the labors of a lot of the researchers who have been doing these studies and have been publishing all these great results.

What we have done is we have created this interface where, especially through what we call our gene journal, our scientists really go through and comb through that literature, read through those papers, and then they come up with a white paper that goes through the criteria that we use of how do we present this information to consumers who have very little understanding of genetics to begin with.

So we have this transparent way of coming up with what we call established research versus preliminary research. The reason we did this is that we first started out with 14 of what then was the ER category, and we left it at that because we felt like we really wanted to stay with these studies that we thought were going to pass the test of time.

But right after we launched we found everybody, including our scientific advisory board members, one of whom is here, really wanted more information. The minute you get access to this, the next thing you want to know

is what more can I learn about myself.

We took that into account, and we decided that we would open up the category a bit more, but we wanted to make sure that we put the caveats around that. There are more studies coming out, and we don't pick these people. The whole thing about learning from your mistakes; I don't know who did this study but it did get published, I think, maybe even in Science. So we just are a reflection of what is going on in the research community, and we give that information out to consumers. We don't judge based on what the phenotype is or necessarily what the category was. We want to be really honest and open about these studies.

The star system that we employ now with our gene journals really gives people, hopefully, the idea that if it only has one star you really have to take it with multiple grains of salt. At one point we were going to have salt shakers and have multiple salt shakers, but you have to run this in front of people and when they see more of something they think that means better. So that didn't work.

So it is really this idea that we are taking

all of this information out to consumers and hopefully putting it in the right light, that this is all new and there is a lot more to learn.

Unfortunately, you can't see it, but when you look at one of our gene journals, and we have maybe three genes associated with something, we leave the line open because we think there could be a lot more genes filling in those slots. Obviously, there is still a lot of research that is going on, a lot of it funded by the NIH, and we want to be a reflection of that and say let's continue to fill in these gaps. Let's get a broader picture and a better understanding of the genetics that we are discovering, and then be able to incorporate that eventually, hopefully, into our overall care.

We do think that in discussions, especially like these, that we do need other definitions of things. Would this be considered a genetic test per se. When you are getting your whole genome, do you call that a test or is it just information. If we have 580,000 data points and we only know about maybe 40,000 of those, or whatever the number is, what do you consider those other data points. We think of them as information about you

that runs around in your cells and now you just have access to it through your computer, which is a different way of looking at it.

Then, the other idea is what is prognostic. What are all these definitions, and how can we work together as a community to come up with a better regulatory means of reviewing it.

Going back to the slide that Teri showed, now that we have our gene journal filled up with all of those great studies, we try to keep that very current. We have people who go through the literature, as I said, and we now have about 78 of these gene journals. I think about 25 of them at this point now are of the established research category, and then the bulk of them are what we consider the preliminary research.

As new studies come out on SNPs that might be in this preliminary category and they look like they have moved into the ER, or the established research, category we do make those changes. That could explain why David saw a bit of a shift in his risk profile, because these things do change.

He brought up a very good point. I point at us

and I point at the other people that are in this industry together, this very nascent industry, that we really need to do our job to work with other organizations to create standards. There are things that we can do, we think, on assumptions that we make. David noted that in his slides, that we do make different assumptions when we come up with these risk profiles, but we should just come together as an industry and say we are going to just settle on the same assumptions. That is a pretty straightforward thing for us to do.

So we definitely plan to do that. We are going to actually be working with the Personalized Medicine Coalition, Ed Abrams and his group. They will take the charge on this as a neutral body to help organize all the thoughts and the desires of these companies and bring this together and hopefully come up with a set of standards. What they are planning I think is by the end of the year, so you can stay tuned. We are really excited about where that will go.

I had planned to go through one of our gene journals, but you don't have to pay any money if you come to 23andMe and just set up a demo account. We have the

ability to show all of the data and all of the tools that we have at your disposal when you sign up as a customer, and we have done this through the family called the Mendels. It is a family of eight people over three generations: grandparents, parents, and then three children.

One of the things we really felt was important from the beginning is allowing people to come together as families and even friends and compare certain things about your genome. We have seen a remarkable uptake in the amount of sharing that people are doing, both at the basic level, which is more just sharing things like your maternal group assignment, your Y chromosome markers, or how much you compare to someone overall holistically across your genome. But it has been phenomenal to see that really going on and how many people are really doing that.

You can look through the slides that we have on data security. That is something we take very seriously for our customers. We just feel like we wouldn't have a successful company if we didn't stress the privacy of the information that we are generating for our customers.

That is a very important aspect of what we are doing.

What I want to touch on is something new that we have just introduced. Every month, practically, we have a new release of our software and our website where we have new tools and new features that are coming out. Within the last month or two what we did release is the ability now to do surveys with our customers.

We started out with fairly straightforward and simple ones: are you left- or right-handed. Even with that one we took a survey that has been used and validated by epidemiologists. It has been really fascinating to see this because not only do we say do you write with your right or left hand or do you throw a ball, but it is how do you sweep with a broom, how do you open a jar.

I found out myself that I'm right-handed but with a moderate preference for left-handedness. I would have had no idea that I did that. When you sweep, if you have your right hand on the top of the broom, or if you open a jar with your left hand, I'm sort of guessing but those are the things. I have talked to other people who ended up being right-handed that they had different

answers on those surveys.

So we are trying to take these validated surveys and move them onto the Web. This is something that we are looking out to the research community and working with epidemiologists to develop these and see what kind of results can we get. We think starting out with things like eye color, handedness, can you roll your tongue, simple things like that that will sort of help us prove this model of can we do research in a Web-based format like this. We don't know. It is really a new experiment that we want to embark upon.

So far we are really happy with the number of people who are responding, and it is partly because these surveys appeal to pretty much anyone because we all, or most of us anyway, can write and we sweep, although it shocked me how many people don't even know how to hold a broom.

So it is really, then, the next step that we are excited about. We just had a study funded by the Michael J. Fox Foundation to do a Parkinson's study. This is going to be far more in-depth, obviously. The Parkinson's Institute in Sunnydale has been studying

Parkinson's disease for many years. They have developed a lot of their own tools for diagnosis.

They are very interested in looking at how can we first move these validated instruments online but then, beyond that, what can we do to develop some tools that might be using Web 2.0 and also using new technologies that would enable any kind of movement disorders people are having that we could measure over the Web.

This is really out there, but this is the kind of thing that Michael J. Fox really is interested in funding, the things that are beyond what we see in the more typical research paradigm. We have had meetings now with SRI, the Stanford Research Institute, where they are working on the Wii game for measuring people's motor skills. We have met with Qualcom. They are getting very interested in health and how different mobile technologies can be used for understanding, measuring, and monitoring disease.

So we are at the early stages, but we are really quite excited about this study. Since then we have had a lot of people coming forward who are

interested in submitting grants and doing work with us.

The whole point is that once we get a number of people in our database and they do show that they are interested in volunteering information about themselves, we think this could be a very interesting mechanism for conducting that type of research.

One of the other things we think is really important when you look at people who do surveys online is they want immediate feedback. That is one of the things we do. When you fill out a survey at 23andMe, you find out how do you stack up to the other people in our database. So it is this instant feedback that we find that people get a lot of satisfaction out of.

So that is an aspect that we always plan to have. You will find out are you of the 12 percent that are right-handed with a moderate preference for left or are you more just all completely right-handed. Those are the types of things we are interested in sharing.

Just to finish, really what this goes back to is the interest in translation. How do we translate all of these wonderful studies that are going on with all of this great information. How do we get that into the

clinic. It does seem to be a bit of a gap that we have in our current system of making this mechanism happen.

The NIH has been great to come up with the CTSA, this new funding mechanism that is forcing major universities to come together with their clinical side and say "You have to work together or you are not going to get the funding at this level anymore."

I think on the consumer side we can help match that and meet that and work together but let consumers be more of an active participant. They get their data and they get access to this information because they want it. Actually, there, I guess, are some studies that [show that] some people, if they are asked as part of a research study, think they should get their data. I think it has been pretty obvious that that is going to be the case going forward.

If that is the interest of consumers, then we want to be here to give them some kind of an access and some sort of an interface to that information. The overall goal is to improve health care and to work together and work with you. We are really excited about continuing this conversation. So, thanks again.

[Applause.]

MS. AU: Thank you, Ms. Avey. Our next presenter was supposed to Kari Stefansson, but he is stuck in Iceland, not Switzerland.

[Laughter.]

MS. AU: So, Jeff Gulcher will be presenting for Dr. Stefansson. Thank you. Welcome.

Presentation by Jeff Gulcher, M.D., Ph.D.

deCODEme

DR. GULCHER: I'm a little shorter than Kari and have less hair.

Kari and I founded deCODE about 12 years ago. The goal was to try to find genes for common disease that might help in predictive diagnostics and also in targeting novel drug pathways, finding out which pathways might be most important.

We set up in Iceland so we could focus on one population. We have collected about 140,000 Icelanders with informed consent specifically for diseases that we ask them about. We also have collected about 230,000 non-Icelandic samples from around the world: Europe, the U.S., Asia.

That is very important because when we make discoveries in Iceland with this very large cohort we want to be able to rapidly replicate and determine whether or not there is validation outside Iceland. We have a whole host of Caucasian, Asian, and African cohorts to do that.

We started doing linkage studies using our genealogy database. That is how we made our discovery for TCF7L2 and for the 8Q region for prostate cancer initially. We have expanded and added genome-wide association data using the Illumina platform from 370,000 to a million SNPs for an individual, and we have genotyped about 45,000 Icelanders now with these high density systems to allow us to do a combination of linkage family-based studies or genetic association studies.

The whole goal of deCODE from a risk diagnostic point of view was to make available some of the discoveries that we and others have made for common diseases, just picking diseases where we thought the relative risk compared to the general population might be high enough to have an impact on prevention and early

detection, at least in some cases and some niches.

That was the reason why we launched disease risk tests for individual diseases like myocardial infarction, type II diabetes, glaucoma, prostate cancer, and atrial fibrillation and stroke. We thought the risk ratios were high enough to perhaps have an impact in certain circumstances.

These of course are using only markers that have been validated or replicated in six to 60 different populations around the world. In some cases it is only in Caucasians, in other cases it crosses ethnic lines. We make that clear in our reports.

Physicians are already using some of this information in their practices to help risk stratify certain patients in certain circumstances. For example, the type II diabetes gene that we discovered, TCF7L2, we include that in a complement of four type II diabetes genes that decode T2. We are about ready to upgrade that to eight genes.

But already TCF7L2 has been shown in a prospectively collected sample cohort, the DPP study of pre-diabetics, to further double one's risk of converting

to type II diabetes within a short period of time. The absolute risk of an overweight or obese prediabetic who is homozygous for TCF7L2 converting is about 50 to 70 percent within three to four years. That is based on the DPP study and the DPS study that was done in Europe as well.

Here is a special niche for a diabetes variant that has been widely replicated in 60 different cohorts but has a certain potential clinical utility of identifying patients who have prediabetes who are at especially high risk for converting. The baseline conversion rate is about 30 to 35 percent. This further doubles that on top of, obviously, the risk factors of prediabetes itself and obesity and being overweight.

ADA has recently addressed this issue of trying to identify prediabetics, number one, and encouraging those patients to lose weight. Then, for those who fail to lose weight who have additional risk factors for conversion, those patients might benefit from pharmacologic management with Metformin and now, recently, with Actos.

When it comes to personal genomics, is there a

role for a direct access to consumers with or without their physicians. We saw a way, like the other companies, to make that accessible. Not to say that individuals work with this information in a vacuum. We encourage them to talk with genetic counselors. We do, by the way, offer genetic counseling and have done so for the last six months of our service for free. But we also encourage them more specifically to work with their physicians because we think they actually have a much bigger role to play when it comes to prevention or early detection of cancer or other diseases.

We have been able to pick and choose some of our discoveries to add into some of these diagnostic tools and risk genetic tools. We have been putting together large systems of information to allow us to do the replications.

For deCODEme, we offer about 30 diseases now. Since there was a large discussion yesterday at the HHS meeting about analytical and clinical validation, I want to convince you that analytical validation for genetics is a lot simpler than analytical validation for CRP or even LDL cholesterol measurements. It is because you can

document the accuracy of your genotyping, whether it is individual SNP genotyping or an Illumina array, for example, like we use.

You actually have 15-fold sampling for Illumina array. You have 15 beads that are assessing the genotype. So there is redundancy that you can make use of in your quality control. We think we are compliant with CLIA, and we are required to do so under our certificate of registration with CLIA. The accuracy can be measured. It can be documented through repeated testing and matching the gold standard that the FDA sets for genotyping, which is sequencing, which we do for all the variants that we annotate, the 100 or so variants that we annotate.

Then we do quarterly proficiency testing, which is also a requirement of CLIA.

On top of that, we do clinical validation and document those clinical validations that we define the way FDA defines it. That is, replicating the markers and demonstrating that those markers are consistent across populations. That is not a formal requirement by CLIA, surprisingly, but that is something we voluntarily add.

In addition to our analytical validation reports, we send the clinical validation reports also to CMS as part of our demonstration that these results are reliable.

When it comes to the genetic markers that we annotate at deCODEme or the individual disease tests, they are all well validated. We don't have any preliminary data or diseases where there might be one or two studies. They need to be replicated widely before we put them into our risk classification.

I should emphasize the relative risk. It is not just that these markers replicate. The important thing also when it comes to clinical validation is how you assess the appropriate relative risk to attach to a particular genotype. What is that based on. Is that based on just a few hundred patients; is that based on thousands of patients.

Most of these variants are actually based upon data sets that we use that include up to 10,000 patients and controls. In some cases it may be 5,000 patients and 30,000 controls, in other cases 12,000 or 17,000 patients and another 30,000 controls. So the bases for these assessments of relative risk are actually based on data

sets that are much larger than are used for FDA approval or diagnostic tests that are approved by the FDA.

Then the question becomes what can you do with that information. Can you combine that information reliably, in a reliable and consistent manner. What we do is we convert each one of these variations, these odds ratios, into a relative risk, risk compared to the general population, to have a consistent reference population to attach that risk.

Then we simply multiply those risks together, because we and others have demonstrated that for the vast majority of these diseases, from the various studies that Teri mentioned, you see no interaction whatsoever, even with these large, large data sets. When we combine our data sets with others, we fail to find significant interaction terms to suggest that these are either redundant or synergistic interactions. Therefore it fits a multiplicative model, and we think we are justified at multiplying these relative risks together in a multiplicative model way. That can be useful to assess the risk for a particular individual.

When it comes to the clinical validation and

the replication, just since Dr. Khoury had questioned that yesterday, let's take prostate cancer. These markers have been replicated in large numbers of cohorts even in our initial discovery papers, where we have large numbers of patients. You can see at the bottom there are 3,500 patients versus 14,000 controls, and there are five or six different Caucasian cohorts that we have in the United States and Europe. Also, on 17q, another 3,500 to 14,000 controls, and so on.

There is Chromosome 8X discovery. The patient population is 10,000 patients, 28,000 controls. I just put this up as an example. We are in a different era now than we talked about yesterday. Now, to even get published in Nature or New England Journal, you have to have wide replication.

That is the new standard today that was encouraged by Dr. Collins and others over the years. Now that standard exists and you can't even publish these discoveries until you have replication in your seminal study.

I should mention that many other groups have replicated these markers as well beyond our studies, for

example NCI and U.K. Cancer. But when you take these relative risks together, you can multiply these individual relative risks, genotype-specific relative risks together. Just like Dr. Collins did in the fusion study and in his genome-wide association study on diabetes with his colleagues, you can multiply these and come up with a composite genetic risk for that particular individual that maps out across a general population like this.

These are the eight markers across a general Caucasian population. About 10 percent of the general Caucasian population has an average risk of two-fold, compared to the general population.

Lifetime risk for prostate cancer is 16 percent. That would translate to a lifetime risk of 32 percent in the absence of other risk factors.

What are the other risk factors for Caucasians. Nothing but family history. The common variants are independent of family history. Less than 5 percent of the general population has a family history of prostate cancer, so that is not necessarily the best screening tool when it comes to risk for prostate cancer. But if

you have this, you have another 10 percent. You have doubling of risk of prostate cancer that is independent of their family history.

We try to communicate these results in a clear and consistent manner. We describe it in terms of relative risk because we think the patients and the physician can understand that much better than trying to create a table of odds ratios. They don't need even need to know what a SNP is and they don't need to know much about Mendelian genetics because these are risk factors. These are not Mendelian determinative risk factors. These are actually risk factors that are much more analogous to LDL cholesterol.

So if you can give a reliable risk score for that individual, they can incorporate that with the environmental and other risk factors that they use on their daily basis. They also convert this into a lifetime risk.

When it comes to consistency among the three different companies, you did see from David Duncan's talk that actually, on the face of it, if you look at the relative risks, we are actually fairly consistent across

the three different companies. He already mentioned that the accuracy of the genotyping seems to be very high. But when it comes to combining the markers, we are doing it in a little bit different way.

We are getting together with PMC to come up with an industrial standard, so to speak, and getting feedback from academia so that we try to do it in a consistent way. But already it is actually fairly consistent.

The differences and the variation seem to be more in those rare instances where you are using a surrogate that is a little bit different for the original marker, the marker that was initially reported. Although, those are still well validated, those extra surrogate markers.

From that standpoint, I think there is a role for additional consistency, but already I think the results are quite consistent across the different platforms. Some of this depends on whether or not they have updated the latest prostate cancer genes, for example, in their profile as fast as some of the other companies.

I gave some examples, but I think David Duncan already did a nice job demonstrating the comparison.

Are these tests useful today? That is the other debate. Francis says that maybe only 10 percent of the genetic variance or less, or a few percentage points, are accounted for, and that is debatable. We agree, though, that the vast majority of genetic information has not been captured by this.

But, is it still useful to identify those at highest risk or not with these tests. We would contend that even for the heart attack gene, the MI gene, that we and others have discovered, it appears to have an effect that is independent of your Framingham score. When you talk about LDL cholesterol by itself, it has very little impact on the AUC. The AUC is still only 55 percent or less with just LDL cholesterol. To push up the AUC you have to combine it with conventional risk factors.

This is a major risk factor that is not being accounted for by the Framingham score and has the opportunity of moving a low-risk patient, based on ATP3 criteria, up to intermediate risk, or from intermediate risk to high risk.

There was a recent prospective study done by Stephen Humphries [in the U.K.] that showed in this 15-year prospectively collected cohort that adding these genetic markers on 9P actually reclassified 15 percent of the patients that were originally classified with just Framingham according to the ATP3 criteria. About 5 percent of those patients overall were in the intermediate category and went from intermediate to high risk category. So it shows how it can actually have some utility.

What would you do differently. As a physician, you would target the LDL cholesterol to a different level based on that risk. That is what is recommended by NCEP3 guidelines.

I gave you my example on prostate cancer yesterday. For atrial fibrillation, we discovered these two markers which are very strong and by themselves double one's risk for atrial fibrillation. Twenty-five percent of us in this room have these high-risk genotypes.

What is interesting is these are by far the strongest-acting stroke genes. If you do a genome-wide

association study for stroke, and our publication will come out in the next few weeks on that, it turns out these by far are the strongest-acting genes. Why is that. Only 15 percent of stroke is due to atrial fibrillation. That is what is thought to be. But it turns out that there is much more atrial fibrillation that contributes to stroke, especially in the cryptogenic stroke category -- that is stroke of unknown cause -- and even in large vessel stroke categories that was not realized until we did these studies.

Now we are doing a very large observational study to demonstrate this, but we estimate that 150,000 stroke and TIA patients are misdiagnosed as having a different type of stroke or a stroke of unknown cause where they really had intermittent atrial fibrillation that is asymptomatic and that can be picked up by extra cardiac monitoring.

If you applied our genetic test and you did the extra cardiac monitoring for a few extra weeks when the patient is discharged from the hospital, based on prevention, putting the patient on the correct drug, moving them from an anti-platelet to Warfarin if they do

indeed have atrial fibrillation on monitoring, that can save the healthcare system $1 billion a year.

Finally, for those who didn't see my case study yesterday, this is me, 48 years old. I have no business testing my PSA, at least based on guidelines, even though my father had late-onset prostate cancer that was considered benign. According to the guidelines, family history only counts if your father was younger than 65. But I was compulsive enough to get it at age 42, with low normal.

When I got my prostate cancer test results back using these eight markers that I showed you, my relative risk was 1.88 compared to the general population. Calculated lifetime risk for a white male would be 30 percent based on this.

I also had extra markers that suggested that I am more likely to have the aggressive form rather than the non-aggressive form of prostate cancer by about 1.3-fold, not dramatic. That prompted my primary care physician to get another PSA test.

This time my PSA was still in the normal range. Zero to four is normal range. But my PSA was high normal

at 2.5. The anagram is coming up later.

My high genetic risk prompted my primary care physician to refer me to a urologist. He was concerned enough to do a biopsy and found that I have prostate cancer with a Glisson score of 6. That is intermediate grade. I will have that taken out by Bill Catalona in two weeks.

Now, this is just anecdotal of course, but once again, can we try to improve the sensitivity and specificity of the biomarkers that we are using today, which we all agree are not perfect. Can we improve that specificity and sensitivity by adding extra genetic information, just like family history is already being used to guide these types of managements. Thank you very much.

[Applause.]

MS. AU: Thank you, Mr. Gulcher. Our next speaker is George Church. Dr. Church is founder of Knome and the director of the Personal Genome Project. Dr. Church is a professor of genetics and the director of the Center for Computational Genetics at Harvard Medical School. He has been at the forefront of DNA sequencing

technologies, including the development of the first genomic sequencing method, in collaboration with his dissertation advisor Walter Gilbert in 1984. His research continues to foster high throughput technologies for molecular biology.

Welcome, Dr. Church.

Presentation by George Church, Ph.D.

Knome, Inc.

[PowerPoint presentation.]

DR. CHURCH: Thank you. I want to thank all of these government agencies, as well as companies that we work with very closely, and also disclose possible influences that we have had.

From the discussion so far, I wanted to say that when we say "personal empowerment requires prior validation," which was a conversation that came up earlier, one of my take-homes here is that a lot of what we are doing in the Personal Genome Project and at Knome and to some extent in my advisory role at 23andMe is research. It is empowering people to do research rather than empowering them to influence their medicine right at the moment.

I think that is incredibly important in the sense that there is a very strong attitude among many people, certainly not everybody, where we want to learn about the world at some risk to ourselves. We will explore the planet and risky areas of the planet individually. We will look at investments. We will look at the Internet. These are all risky environments in different ways that affect your quality of life, and they are probabilistic decisions that aren't necessarily any more complicated or less complicated than genetics, and they are moving targets.

This is the other end of the spectrum, I think, from the big four or five we are talking about here today, where we have various ways that people are doing their own genetics. Many people know about the genographic project, which is mainly ancestry. But in addition, Hugh Rienhoff was on the cover of Nature for trying to understand his daughter's illness, and he is doing this basically in his home.

But what is happening is that there are people that, rather than hiding from their personal genomics, for which there is no cure, they are embracing it, they

are becoming activists, and they are saying we can do something for our family by doing research on our ourselves and people like this, ranging from my colleague Doug Melton, whose family has diabetes, to Hollywood blockbusters about lipid biochemistry that Nick Nolte became, representing Augusto Adone and his son. Nancy Wesler. We have already heard about Michael Fox and so forth.

Next slide. So, in this context of course, all of those and some of the people we have heard about today are saying privacy is not their top concern. But even when it is, there are many ways that privacy is compromised when you put things anywhere other than in a vault. You can have a laptop theft where 26 million veterans' data got out. You can get a case where a 15-year-old person wanted to know his anonymous sperm donor father and took a cheek swab and did a genealogy which narrowed it down to an individual that he found and confirmed was his father.

There are many, many ways that data get out, and it is unrealistic to overpromise. We certainly want to try to make it as private as possible.

When we talk about the research landscape here, we have standard research on the far right here, where we have open access as long as there is no trait data, such as the 1,000 Genome Project HapMap, and we have various types of approaches that are increasingly returning data back. We have already heard about the Reveal study with my close colleague and so forth.

But typically, the data are kept de-identified or safe from the individuals that donated it.

At the other end, you have it only available to the individuals with marginal ways of getting it into the public domain. Then we are exploring ways in the middle here where we can make it both publicly available, connecting DNA and traits, and yet not overpromise on privacy, particularly recruiting people who have passed an exam with 100 percent on the questions. That is Item No. 4 here.

One of the goals of this project, which has had IRB approval since 2005, is to really try to get ahead of the curve. Of course, the curve has well caught up with us at this point. But the idea is to bring technology to bring down the cost of not just the coding sequence but

the regulatory data -- by "regulatory," now we are talking about RNA regulation, not the kind of regulations we are talking about here -- that Teri mentioned. Maybe 6 percent is coding in GWAS studies, but closer to 90 percent in the rarer diseases that populate online Mendelian inheritance.

We want full subject participation, which is not unusual in this context. We have multiple samples to make sure we have the identity. We have open access. We have a trait questionnaire. We have stem cell RNA I will mention in a moment, and we have now IRB approval to scale up to 100,000 individuals.

We are focusing on sequencing, and I think Ryan Phelan will talk in a little while. This is one of many tests that constitute the best of the genetic diagnostics, but this illustrates that, in contrast to the big three that are producing chip-based analyses, when you really want to go into detail on a test like BRCA1 and BRCA2, you are typically talking about sequencing, not chips. That is not necessary forever, but that is typically the practice now.

DNA Direct has something where you actually

will see causative alleles which change the reading frame for tumor-suppressor like BRCA1. This has to be very carefully interpreted at the DNA sequence level because the consequences are very serious even the preventative sense, where people will do a bilateral mastectomy if they trust the interpretation of the data.

Now, we have alluded to but haven't really touched on yet this next generation sequencing, which has changed our perspectives of what is possible tremendously, possibly by a factor of 1,000 drop in price. You will see this in a later slide.

There are at least two classes of chemistry. We are trying to produce a platform that will support multiple versions of each of these classes of chemistry based on DNA polymerase or ligase. Rob Mitra helped worked on the polymerase version in 1999, and a couple of companies, Illumina and Intelligent Biosystems, use this.

The same thing can be done for ligase. We are using fluorescently colored monomers or multimers which can be discriminated by these enzymes. This is something that Jay Shendure and Greg Porreca developed.

Now, in addition to those commercial

instruments, we have an instrument which is kind of at the fringe in between academic and commercial which we call a polonator which is intended to be an unusual model and which is completely open-source hardware, software, wetware. We are just opening it up to the community so they feel empowered to change any part, and it is intended to be easily modular.

Now, maybe only 5 percent of the research community will want to change it, but that 5 percent will greatly aid the other 95 percent.

So this is $155,000, which is about four times less than our previous contribution to the applied biosystems solid device, which is $600,000, and similar to even lowering in prices of the reagents and reagent use.

Next slide. What does that kind of technology result in. It results in plummeting costs which are faster than the already very rapid Moore's Law for Computing. Moore's Law for Computing is about a 24-month improvement in service for a given price point for computers, and this is more like a six- to 12-month doubling time, going from a fairly low estimate cost of

$100,000 per million base pairs towards the end of the Human Genome Project, plummeting -- this is a logarithmic plot, as you can see -- down so that we are getting close to $1,000 a genome very, very soon. Multiple technologies are going along this pathway at slightly different points.

We can see how this plays out in the consumer market here in the genographic project, which is arguably the most popular out. Two hundred thousand people have done it. It has a very high price tag per base pair or per bit of information, but still people are very curious about their ancestry and they are willing to pay a lot, $99 for 12 bits of information.

DNA Direct has very high quality and medically actionable information, mostly done with DNA sequencing technology which historically has been expensive but has been plummeting, according to this plot here.

We are already familiar with these. Then, the Personal Genome Project has a cluster of four points here because we are not just doing genomics, we are doing coding regions, regulatory, microbiomics, and so forth. But they all have roughly similar price per mega base

pair.

Then Knome is the only company that really offers full genome sequencing. It is currently $350,000 and likely to go down on that same curve very soon.

So it is not just genomes, as David mentioned in his talk earlier. There are environmental components which are very important. When you say "personal genomics," you should be thinking about the regulatory elements which might be less expensive and more interpretable if analyzed at the RNA level.

Some of the environmental components can be measured either by measuring the microbiological components, allergens, microbes, viruses, or their impact on the immune system, which, rather than being a spike of microorganisms, it might be clear from the system will be a longer term persistence leading to traits. So we don't just go from genome to traits. We go through this regulatory and environmental filter.

Next slide. In order to get at some of these RNA regulatory interactions with the environment, in the Personal Genome Project we have included multiple cell types from adults whether they are healthy or diseased,

and we don't do it by assaying all of the different tissues from the PGP volunteers. Even though they are really gung ho, they really draw the line at a thousand biopsies.

[Laughter.]

DR. CHURCH: Instead we take one biopsy from the skin from which we have established stem cell lines, and we are making these available to the community, from which you can reprogram to almost any tissue you want. This is of course a very fast-moving target as well.

We want to be able to do biology on these individuals as well as inherited germ line genomics. At the extreme of that is looking at the microbiological components in general, viruses and bacteria, and not necessarily the whole genome but selected parts. Just like we might want to do different assays for the inherited genome that go beyond SNPs, we might want to go beyond SNPs for microorganisms.

Here we have studied the resistance settlement to 18 different major classes of antibiotics over 140-some days in some of the Personal Genome Project volunteers. A big solid blue means that each of these

isolates along the X-axis is resistant to multiple antibiotics along the Y-axis. This was a surprising result and was actually an outlier both for this individual and for other individuals done on the same day. But this is the kind of background information that you could do by highly targeted analysis of microbiomics.

MS. AU: Dr. Church, could you just wrap it up in about 15 seconds?

DR. CHURCH: The next slide is the last slide.

The questions I wanted to add to the questions that were given are, how do we fund these association studies in education. Is there a role for direct-to-consumer companies. How do we celebrate and incentivize the best protocols, not just scare the worst and reinforce the oldest.

What about do-it-yourself genetics; is that going to be completely outside the direct-to-consumer we have been talking about. There is this risk of gene information. There are many other things that people do that are probabilistic that I mentioned. There is the risk of not educating. I don't think anybody is seriously considering that. What kind of model do we

have. Is insurance an interesting model, where healthy people like David still have a finite risk. Thank you.

MS. AU: Thank you.

[Applause.]

MS. AU: I will turn it back to Steve and Rick for a little bit. Ms. Phelan is going to talk about the Secretary does his thing.

Introduction of the Secretary

Steven Teutsch, M.D., M.P.H.

DR. TEUTSCH: As all of you can see, we are extremely fortunate today to be joined by Secretary Leavitt. As many of you know, the Secretary has shown enormous initiative in the area of personalized health care, for which we are very grateful.

This Committee, Mr. Secretary, has been working very diligently for a long time, and we are really grateful that the report and efforts that we have done have reached your office and are getting the kind of scrutiny that we hoped they would. We really appreciate your leadership.

For those of you who aren't aware, the Secretary was formerly governor of the State of Utah and

born and bred in Utah, so it is a particular privilege for me to introduce you to the group. We look forward to having your thoughts. Thank you.

Remarks by the Secretary

Michael O. Leavitt

SECRETARY LEAVITT: Steven, thank you very much for your leadership of this group. I had a chance to meet with Reed Tuckson a couple of months ago at the interchange, and I didn't have a chance to publicly thank him but I want you all to know I appreciated his service. I expressed it to him directly.

Thanks for indulging my unscheduled visit. I did want to just come and thank you for your service. This is an area of quite particular interest to me. We are struggling with so many different issues where there is a need for balance and finding that place between fostering innovation and, at the same time, giving people the sense of confidence that they need.

It is so seldom that we are ever close to the curve or ahead of the curve, and I think many of the issues that you are dealing with are on the leading edge of the curve. There is a good possibility we will be

able to stay somewhat ahead in terms of the policy decisions.

I was very pleased and appreciative of all the work that went into the passage of GINA, and I want to acknowledge my great admiration for Francis Collins. As I'm sure all of you know, he is not only going to be leaving the panel but also HHS. He is going to go on to do great things and we will all have a chance to see him and be involved with him.

Francis, I just want to tell you how much I have valued our relationship. I have told you that a number of times privately, and I want to say it publicly, too.

DR. COLLINS: Thank you.

SECRETARY LEAVITT: Thanks for all your contributions.

I will just mention, in the same spirit of staying ahead of the curve on these policy issues, today it just happened on my desk landed an FDA release. The U.S. Food and Drug Administration has approved a novel genetic test for determining whether patients with breast cancer are good candidates for treatment with the drug

Herceptin.

We are going to see a lot of this. We [need to] have the capacity to stay ahead of the policy issues related to it, and there are so many still to be dealt with. I have spent a lot of my time as Secretary dealing with what I think is going to be a convergence, a convergence of information available electronically that we can use to provide patients with unparalleled information about the quality and the cost of their health care. I think that will lead us into an era where we will be able to make judgments on the effectiveness of drugs and effectiveness of different procedures.

I was in Singapore a few weeks ago and saw a collaboration that is going on there with NIH. We were looking at the various generations of being able to sequence and essentially lay out an individual genomic profile. It again called to my mind how rapidly this is changing. We talked about the speed with which that could be accomplished over the course of just a few years.

It is evident to me that at some point this will be very common. If we don't have the ability to

manage this information in a standardized way, if we don't have the capacity to protect the privacy of those, that there will be a great opportunity lost.

I think we are ahead of this curve, and so I want to thank all of you for being willing to struggle with these quite significant dilemmas. It is of great value to me as Secretary, and it will be to future Secretaries.

Steven, I didn't want to disrupt the meeting too much. If there are subjects that your colleagues would like to inform me on directly --

[Laughter.]

Question-and-Answer Session

SECRETARY LEAVITT: This would be a very good time to do that. If they have a question or suggestion, I would love to interact a little with your group.

DR. TEUTSCH: Please do. Comments or questions? As you can see, the topic is of great interest. We have a standing room crowd. Please take advantage of this opportunity to engage the Secretary.

SECRETARY LEAVITT: In this kind of a crowded council generally there is a fight.

DR. TEUTSCH: So far so good.

[Laughter.]

DR. TEUTSCH: Julio.

DR. LICINIO: Yes. I have a comment. I'm Julio Licinio from the University of Miami. As we have seen, particularly in today's meeting, there has been a lot of advancing genetic information being made by the private sector directly to consumers. The special academic health centers and the more traditional side of medicine have been a little more hesitant. The two sides look at each other with some degree of suspicion.

Do you have any ideas or thoughts of how we can move ahead with 1) the direct-to-consumer approach, and 2) the traditional medical approach?

SECRETARY LEAVITT: I won't resolve that today.

[Laughter.]

SECRETARY LEAVITT: But I do think that that is the type of question I was talking about. How do you give people the sense of security they have, at the same time allowing innovation to go forward. I believe that if people are given information that is high quality and that is consistent they will use it in a way that will

drive their own interest and, in doing so, will drive the quality up and the cost ultimately down. I think having the capacity for consumers to have access to it is going to be of enormous importance.

I don't want to weigh in on either side of that today except to just acknowledge the struggle and to say I think it is a positive struggle because it is in the tension between those that both sides of the debate will ultimately be improved.

I don't have anything beyond that to offer except to say the struggle is good. It will create a positive outcome because both sides have legitimate interest and legitimate points of view. I think that it is often the case that consumers are underestimated in terms of their capacity to sort through these things, and I think there is often a sense of well intended protection that we want to provide that sometimes can constrain progress. Somebody needs to be pushing the envelope a little, and yet, at the same time, someone needs to have the brake on just enough to keep us on the road.

DR. COLLINS: Mr. Secretary, can I ask you a

broad, overarching question? First of all, thank you for your very kind comments a moment ago. It has been an absolute privilege to be part of this Department and to serve under your leadership. To have someone as the Secretary who has such an interest and such a fund of knowledge about personalized medicine has been just truly gratifying, and I think I speak for all the people on this Committee in saying so.

SECRETARY LEAVITT: I have had great teachers.

DR. COLLINS: One of the reports this Committee put out was on reimbursement for genetic tests. I think as we are both excited about the potential here of personalizing prevention, we are also wondering how that is going to get implemented in a circumstance where, at the present time, our medical care system seems to be more devoted towards reimbursement for actual disease than it is for covering the possibility of prevention.

At the same time, I think many economic models would say we have to change that if we are going to do something to rein in what is otherwise a really scary curve of what proportion of our GDP is going to go to health care.

So, from where you sit, can you project at all what the opportunities are here for taking the science, which is putting us in a position to do a better job of prevention, and actually putting that into an economic framework that will enable implementation across the board, not just for people who have a lot of their own personal resources to invest in this with their own pocketbooks but as a more general public health strategy.

SECRETARY LEAVITT: I will just say it has to happen. It is just a function of, really, when people are confident enough in the science and we have an economic model that will demonstrate the capacity for this to provide long-term savings.

I'm aware of this issue. I get lots of mail about it.

[Laughter.]

SECRETARY LEAVITT: I suspect some from people in this room.

I know CMS is still wrestling with this. I had a briefing and a conversation not long ago where they laid out what they saw as the competing considerations. But it must have happen, and it ultimately will. I just

think it is a function of when are we confident enough with the science and when does the economic model warrant it.

One of the things that gets into this discussion that is unfortunate in my mind is the way the federal government scores its budget. We don't score prevention very favorably. We don't give credit in the development of budgets in the scoring model for good, thoughtful, preventative measures. I believe that has to change across the board, and that will be part of what happens. It is not likely to happen in the next 197 days, but I think it will happen.

DR. TEUTSCH: Paul.

DR. BILLINGS: Mr. Secretary, thank you for your work on GINA as well. I was going to ask you how this Committee can be optimally useful to you in your last months of tenure and how you think we might be ultimately useful to the incoming Secretary.

SECRETARY LEAVITT: The report about the oversight of genetic testing, that is a very useful tool. It helps very much for a secretary to have a place where he can toss a difficult question and say "Give me the

best solution here." I think you can expect that the work of this panel will just increase. There is an endless number of thorny, difficult policy issues that I believe I and future secretaries will be addressing to this group for solutions.

So I would just say what you can do is just show up and give your best advice, because there is going to be a lot of it required.

DR. TEUTSCH: Muin.

DR. KHOURY: As a fellow federal employee, we probably haven't met, Mr. Secretary. I'm Muin Khoury from the CDC National Office of Public Health Genomics. I just wanted to thank you for your leadership the last few years. I was going to follow up a bit on the oversight report since the Committee has really worked hard over the last few months and gave you that report. There is lots of good information.

It is befitting that you would show up in a session that we are talking about personal genomic services because the field is moving so quickly. As you started saying, we need that balance between innovation and also, at the same time, high quality information to

the consumers and the need for oversight and the federal government to do just the right thing, not too much of one thing versus the other.

I was wondering whether or not there is going to be any movement on that report during the next few months.

SECRETARY LEAVITT: The places that it helps the most are in the debate we just talked about where you have money decisions being made based on the movement of science. There is little question in my mind, as I suggested, that we have to ultimately deploy a model where we can use these tools in prevention. The issues really will boil down to when does the science reach the point that we can reliably depend on it and when can we get government policies aligned with it.

I don't know how close we are to that delta because there is a lot of thought being given to it other places in the Department. I don't want to either bias or, for that matter, improperly inform about it. So I won't say more except that I do want you to know that the report is both useful and being used and moving us toward the point where those cross in making that determination.

DR. FITZGERALD: Thank you, Mr. Secretary, for coming and being with us today. A quick question, somewhat logistical, very practical, but I think one that is becoming more and more important to this Committee as we do exactly what you say, which is to try to address the multiplicity of issues.

Logistically, in the past our responses have tended to be focused on these larger reports, which I'm sure are very helpful to you if you have insomnia.

[Laughter.]

DR. FITZGERALD: But it might be also useful if we focus on perhaps more brief responses, more directed responses, things that might have to be done in between our semi-annual meetings.

The question that we have been wrestling with a little bit yesterday and we will wrestle with a little bit today is, are there other ways in which we could get information to you in a timely manner, perhaps in a more focused way. Would that be helpful?

[I would just] say, too, Rick and Greg have been wonderful in giving us direction from your office and helpful advice on how we could best serve the

Department of HHS.

So I'm just wondering, is that something that we should be looking at more or are these reports really the way we should be focusing our efforts?

SECRETARY LEAVITT: Let me be truthful about this. The executive summary of a report is the most important thing to me.

[Laughter.]

SECRETARY LEAVITT: I don't wade through the depth of things I don't understand. I do find the summaries very useful.

To be honest with you, where I turn is to Rick and Greg, who are very much involved in helping me have the information I need and in some cases defining the questions I need to ask. So let's pose that to them.

[Laughter.]

DR. CAMPANELLI: The question was are the longer versions of these things or are there more targeted things. I think right now I would say that for our tenure here that we have a lot to chew on in the report that you have given us, and we are chewing on that.

But I think it is a good question looking forward. I think we certainly have the kind of relationship developed that we have where we could come to you directly with particular questions, and in the past sometimes we have. We have targeted more specific questions.

From my perspective, and Greg, I don't know if you would want to say anything more about that, we really would avail ourselves of both of those methods if it was convenient for the Committee to look that way.

SECRETARY LEAVITT: I would be interested to hear Greg's response, but while he is coming up near a microphone --

[Laughter.]

SECRETARY LEAVITT: I have found that these larger reports often anticipate questions that haven't yet been posed, or at least they are not mature or ripe yet in terms of policy. Generally, I will end up with a policy question that frames up an issue, and it is very helpful to have one of my colleagues to say "We had a very thoughtful group look at that. The SACGHS has actually examined it and here is what they said." They

may then extract some thoughtful piece from that report and I get it in a two-pager and they write it at a level I can understand it.

So I don't think you should assume that because it is big and thick that at some point in time the essence of matters related to direct policy don't find their way to the Secretary. They do.

DR. DOWNING: Now you have revealed all of the secrets about how it works.

[Laughter.]

DR. DOWNING: I think the one part that is not told is the community that develops within the organizations and across the agencies. This forum, this leadership, and your vision I think has created, at least in my 15 years of public service, a very unique opportunity to share not only the science and the technology but the human elements of what these important challenges present.

It is still a little fuzzy sometimes as to how the decision processes ultimately work, but I think that what we have tried under this initiative is some new ways in which the confluences of the challenges that face

every agency, and in many aspects the corners of the Department that I didn't even know of, collectively get to a common place.

Our first conversations that we had with you almost two or three years ago now really were all about that, and the visit to the mountain, and how to bring the community to a new place of understanding. It won't be the happy place that everyone envisioned in their own dreams but the aspects of getting there collectively. That journey is a really important part of the story.

I think we have valued this forum as an important way to ask critical questions and learn from all of you and to help us keep in front of everything that is coming. I think in your role [as] the Secretary to convey that to those who follow, that will be an important asset for that challenge of science and technology and the aspects of human health.

SECRETARY LEAVITT: You referenced the mountain. When I was governor of Utah, Steven, out behind the state capital there is a peak. It is called Ensign Peak. You know well, then, that it is a favorite place for people to hike. At lunch often, for my

exercise, I would leave the state capital and hike to the top of this peak. It was about a 45-minute forced march and your heart was pumping pretty good by the time you got to the top.

But it wasn't just the exercise I enjoyed. It was being able to be up high enough that you could see the entire expanse of the valley in the Salt Lake City area. You could see freeways and schools and universities. You could see hospitals and houses and playgrounds. You could just see the way all the forces of a society have to come together to make a community. It felt like a great place to think because you could just see so much of the way things interact.

I would say that has been the significant privilege of being governor of a state or being Secretary of Health. It has allowed me to see enough of the confluence of different things that a picture of how this is going to unfold begins to form in one's mind.

I can see this, and I know you can, too. It is a much different future than we now live in, but it is happening one dot at a time. The key is figuring out how to connect them all. We spend a lot of time with

electronic medical records. Why? Because it is the electronic medical record that allows us ultimately to have the quality information and the ability to provide the personalization that will ultimately use this tool.

Moving all of these along in parallel isn't a neat, clean process. It doesn't happen in an orderly way. But you can begin to see it form up. Having the capacity as you come to a point where you have to connect two or three of these dots, having a group like this to be able to not just have a place to toss questions but to have a body of thinking that can inform various parts of it as it comes together, is a very important thing.

I think my message here is don't think you are just responding to a question from the Secretary. What you are doing is creating a body of information and thinking that will connect a lot of different parts of this system as we move into the future.

I'm disrupting your meeting longer than I had intended to.

DR. TEUTSCH: Thank you so much for coming, Mr. Secretary.

SECRETARY LEAVITT: Thank you.

DR. TEUTSCH: It is a privilege, and we do appreciate all your leadership and support of all the agencies. You should know that the staff that support us is equally terrific.

SECRETARY LEAVITT: Thank you, thank you.

[Applause.]

Personal Genome Service Providers (Continued)

MS. AU: We will continue on with the session. Thank you, Dr. Church. I'm sorry we abruptly stopped you.

Our next speaker is Ms. Phelan. I want to thank her for holding her session while the Secretary was able to come visit with us for a while.

Ms. Phelan is the founder and CEO for DNA Direct. She has been a strong consumer health advocate for the past 25 years, having started the first medical library for consumers in 1978. Previously, she was the founding director of Plain Tree, a nonprofit consumer health care organization, and founder of Direct Medical Knowledge, an extensive consumer health website which was acquired by WebMD.

We thank you, Ms. Phelan, for being here.

Presentation by Ryan Phelan

DNA Direct

[PowerPoint presentation.]

MS. PHELAN: Thank you. It is an amazing honor to be here today and a pleasure to hear Secretary Leavitt speak as well. Thank you for allowing me to be here today.

I started this company now, DNA Direct, in 2004, and I spoke with many of you here in this room in the year before I actually developed it, trying to think through everything from the ethical issues involved to the clinical and scientific issues to actually the challenges of doing Internet commerce. It is really a pleasure to see over this period of time how much has changed in our industry and really, I believe, how progressive society is in moving in a positive way.

The mission of DNA Direct is clearly to bring the power of personalized medicine to patients, consumers, and providers. As mentioned in my introduction, I have been involved in health care information really for 30 years. I started the first medical library for consumers in 1978. This truly is an

extension of a belief and a commitment I have to helping consumers take an active role in their health.

We launched in 2005 by working with a very distinguished and important group of scientific advisors who really looked at how could DNA Direct innovate in this whole field without innovating around the science but innovating around the delivery medium which we were using, which was virtual medical genetic testing, and using standard clinical protocols but Web-enabling them.

That meant that we would have everything done under the medical oversight of our medical director. It meant that with his cooperation we would create very clearly guidelines for our genetic counselors and follow that same procedure from beginning to end, starting with informed consent, all the way through the test facilitation and the interpretation.

DNA Direct now currently works as well with healthcare providers significantly as an extension of their healthcare services.

The physician is at the core of a lot of what we do. We do not always facilitate the test. Much of the time we work with physicians where we are doing

purely just the counseling and interpretation services. Of course, DNA Direct is never the lab in any of this. We work with all CLIA labs, depending on the type of test that we are offering.

Our medical genetic testing ranges from everything from standard prenatal testing to carrier testing, to currently drug response testing. I'm sure Herceptin is something that we will be adding to that list with the new FDA approval.

We look for, in everything we do, whether or not this is a test that is going to be clinically actionable. Is there something that a consumer can do with this information. We spent yesterday defining what that really means and how these terms can be used and how they can be confusing. But I think we really all know at the end of the day whether or not something has medical and healthcare significance.

I'm going to just walk you through a few slides very briefly about how our testing works. For any of you who have seen our site, anytime anyone goes through a testing area there is significant pre-test information to really help consumers understand the pros and cons of

testing. DNA Direct is clearly committed to making sure people know when a test is actually going to be helpful to them and when it might not.

Our questionnaires actually do two things. One, they determine where testing might be appropriate, but secondly, the information we glean from that regarding personal or family medical history for a condition is used to actually build a personalized Web-enabled report with their test result.

All of our customers' medical charts and questionnaires are reviewed, along with the test result, by a medical geneticist before we release any result to our consumers.

From the patient side, testing is easy and can be facilitated with anonymity with a unique identifier that is sent to a CLIA-certified lab.

All of our tests are provided with clear transparency regarding our pricing. DNA Direct does not market any lab fee. We pass that cost directly on to our customer, then charge for our interpretation and consulting services.

This is just an example of a report for, in

this case, a BRCA result that is positive. The test result, as I mentioned, is customized based on their family history. All of our BRCA customers go through an in-depth pre-test phone consult as well with our counselor as well as the online experience. Obviously, we want to identify that the right person is getting the right test and that it is really appropriate, and that phone counseling is going to work for this particular patient.

For many of our customers, one of the things that we are constantly talking about is whether or not they would prefer to see an in-person genetic counselor. We have a network of over 60 genetic counselors that are affiliated with DNA Direct where we can refer somebody if we actually think that a phone consult is not as appropriate as an in-person.

All of our reports include a physician letter that is two- or three pages. We heard that from some of the physicians yesterday. The last thing they want from a patient is a ream of useless information. What they want is really specific, easy-to-read fast information about the clinical guidelines and the significance of the

test for that patient.

All of our data is secured from the get-go of the company. We look very clearly at SSL protocols to make sure that we set up the system. Our genetic data regarding a result of a patient is kept totally separate from any Ecommerce transactions. So basically, the shipping, billing, and personally unique identifiers are kept in one server and another where all genotype and phenotype correlations are.

Just a few minutes about why consumers use our service. First of all, they often come to us because they have had a problem obtaining a genetic test for one reason or another. Sometimes it is purely geography. Everyone in this room knows that there is a dearth of genetic expertise out there, and as consumer awareness increases around this there will continue to be this bottleneck of services.

For some, they referred us to a physician purely because a physician doesn't want to be doing the interpretation. Physicians are not paid in their eight-minute visit to be really taking significant time to do the kind of consulting or counseling around family

history and everything else.

Some purely want anonymity. I suspect that may change somewhat with GINA, but the truth is anonymity is not just about genetic discrimination. Sometimes it is about personal privacy.

I thought I would take a second and explain our experience with customers. First of all, 46 percent of our customers have a personal family history for the condition that they are testing. It is a very large number. Eighteen percent have a personal diagnosis with the condition. Twenty-one percent have a known family mutation. A combined 53 percent have both.

A really important take-away here is 34 percent of our customers across the board -- since we started the company it has been anywhere from 35 to 40 percent -- test positive for a mutation.

Now, for those of you who are geneticists in this group, you will probably recognize that in a traditional genetics clinic positive mutation rates probably run much closer to 5 to 10 percent in the general public. By the way, what that means is DNA Direct is testing appropriate people for clinically valid

tests.

I would like to end on this one slide, which is something that I showed yesterday. Unfortunately, this Adobe Acrobat Reader is not reading this correctly, but those little square boxes, or rectangles, were meant to be check boxes. What I'm trying to do here, and I'm really trying to help the Committee think through this whole field of genetic testing, [is show] that not all genetic tests are equal.

I started at the bottom of this triangle with serious diagnostic testing, like Huntington's disease. Most of us could agree that that is probably best facilitated in a bricks-and-mortar setting with in-person evaluation by genetic experts and very clear physician oversight.

But as you go up this ladder, you have to go up this ladder and start to think [more broadly] about the implications for genetics. Right up the ladder I say predictive testing for serious health concerns. These may not be 100 percent predictive like Huntington's, but they certainly have very clear clinical indications. BRCA is just one example.

At DNA Direct, we believe, obviously, that this can be done with a genetic consult by phone. It does not have to be done in person. In fact, DNA Direct is under contract with Moffett Cancer Center where we do, for part of their research with black African women, all of their phone consult for pre- and post-test consulting as part of their research trial.

The academic centers already are acknowledging that phone consults can work very well and Web-enabled education is clearly going to be a wave that is moving and integrating into health care.

As we go up this ladder, we look at genetic screening for very common things, carrier testing, risk screening, risk assessment, drug response for pharmacogenetics for Warfarin or Herceptin. That probably doesn't need to be done in a physician's office. If we want to look out of the box at this, we might want to say that a healthcare insurance plan could be looking at how to target particularly select populations and making sure that they could get a genetic test easily facilitated through the Web or through phone as appropriate.

But as we continue go up this ladder to genome-wide arrays and to full genome sequencing, I think that is where we really have to start to think out of the box. Our company doesn't provide those services, but what we do is provide support services for anyone who has had information gleaned from one of these tests who may have a personal or family history where they want to test further.

But what I think is important here as we look at this area is we have to question whether or not there should be a different guideline for people who are engaging in genome-wide arrays or full sequencing for different purposes than clinical genetics.

I think that this is something that we are not just wrestling with here in the U.S. I just came back last week from the United Kingdom's Human Genetics Commission. They too are wrestling with these same issues that every one of you as Committee members are thinking about. They are calling for a voluntary code of practice regarding the delivery of genetic information services.

One of the things they were very clear to say

is this is a regulated industry, whether you are in England, Europe, or the U.S. We clearly saw that with the recent California cease and desist letters. There is regulation going on here. The question is, what kinds of further regulation are needed and is there a place, and I believe there is, for creating a best code of practice that I believe industry here, right now, is working very closely together to try to move this field ahead in a really responsible manner.

I appreciate your time. Thank you.

[Applause.]

MS. AU: Can I ask all the panel members to come up to the front? We are going to have 30 minutes for the Committee to ask questions of the panel. I ask that you keep your questions concise and single questions so that everyone can have a turn, or else Yvette will be on you.

I think Kevin had his hand up.

Roundtable Discussion with Personal Genome Service Providers

DR. FITZGERALD: I thought I would be way down

the list. First of all, thank you all very much for your presentations. I'm limited to one question. However, I didn't hear any limit to the number of comments I could make. No, I'm only kidding.

[Laughter.]

MS. AU: You heard the "concise" part.

DR. FITZGERALD: First of all, let me thank you for hearing over and over again a desire on your part to be engaged in a conversation. One caveat, though, which I think is important to acknowledge on both sides is in any conversation there is always the possibility, and with this group the probability, that you will hear something you don't want to hear or that you don't like to hear. But that is part of being in a conversation.

So the idea I think in the end is that we are all hopefully on the same page and that is, as many of you have mentioned, to try to improve health care, to get much of this to the public in a way that the public can use this information to better improve their health and their lives.

To that end, I would like to make one suggestion to Professor Church. On the slide you used

where you have all the various researchers and people who are involved in this because of personal influences in their own family, their children or themselves, with the disease, it might help to achieve that balance that Secretary Leavitt was mentioning if you also include a picture that came from a Wall Street Journal story on December 15th, 2007, about a father who is giving his seven-year-old son who has cancer 44 pills a day, most of which are not prescribed by the doctor, because he is using this very information that is available on the Internet.

So it does work both ways. I'm not saying that you stop something just because someone can abuse it. On the other hand, you don't do something just because you can because there has to be that balance.

On that end, a question. Many of you are involved in for-profit enterprises. I am not against for-profit enterprises per se. However, this is health care. This is not selling cars. So my question to all of you is, would you sacrifice your fiscal bottom line of your company in order to achieve the goals that you say that you have, which is improving the health care of all

people, particularly in the area of access to your services?

MS. PHELAN: I would answer that from DNA Direct very clearly. From an investors' perspective, we have always sacrificed the bottom line. I believe that that is true because we are constantly thinking about how to provide a quality service in a responsible manner, and that is not always about an ROI.

MS. AVEY: From the 23andMe perspective, that was something very important early on when Ann and I started the company. We felt very strongly that we needed to stay in control of the company. For that reason we didn't take the typical venture capital investment. We were lucky to have supporters like Google and Genentech come forward and give us more of a strategic investment as opposed to them wanting to control anything we were doing. They really support what we do, but they don't have short-term objectives as far as financial reward. Obviously they are doing very well

So it is good for us because it gives us the control. It is only Ann and myself and Esther Dyson on our board. We control the company. We feel very

strongly that we need the runway and the time to do this right. We don't have to have short-term objectives coming at us from other investors.

As I mentioned yesterday, we did consider trying to have a not-for-profit arm of the company to do things in parallel with what we are doing on the for-profit side, but you do find when you try to explore that, first of all, it is very hard from a tax perspective to have two different companies or two different sides of a company. It is also hard when you want to do research in a very big, global way to try to separate out the two.

So we did think long and hard about that, and so I do feel very strongly that we are going to have a social mission. We want to do continuing research. We are going to look for funding to help people pay that can't afford it.

I think there is a lot of that incentive and that drive within the company, but we also have to hire engineers and they won't come to work for a not-for-profit, typically. That is our challenge.

DR. GULCHER: We are involved in a publicly

funded project where we are doing the genotyping at cost with a 1 million-chip array for several hundred individuals in a cardiovascular project. That hasn't been announced yet. But we are also providing back to the participants their deCODEme results on a voluntary basis because the researcher thought it would be very useful to give something back that would profile these patients beyond the research aspects of the study, which are unrelated to deCODEme.

That is one example where we are doing it at cost and providing that information and looking, regardless of whether or not the patients have the ability to pay, to see is this an interesting demonstration of how people might use this information in parallel with the research aspects of the contract.

DR. STEPHAN: I have been working in the academic, nonprofit space for the last 15 years doing research to identify the genetic drivers of disease. Implementing genotyping as a service just doesn't fit within the academic, nonprofit model, for the most part.

I would throw back across the fence to you what proportion of the service-based medical infrastructure is

not for profit. Physicians operate on for-profit models. All diagnostic companies operate on for-profit models. I wouldn't say that that is a negative per se associated with this space.

MS. AU: The next question is from Julio.

DR. LICINIO: I have a question to do with not really the accuracy. I'm in a medical school. You teach people and you use whatever research is out there towards health care. This type of information is coming from whole genome association studies and genes that we didn't even know existed before these studies, like one of the obesity genes that came in Science last year. These things come up, and it is interesting but it is not yet something that we apply in health care.

Then you have the direct-to-consumer information. The paper is out there in Science. We had a discussion about this yesterday. There are even things that come out in Science, Nature, and the New England Journal of Medicine with a lot of known replication.

When the microarray data that came out was on the cover of Nature, the best microarray for cancer identified in different profiles, there was the same type

of work in New England and not a single gene overlapped. There were different profiles. Sometimes, even when the work is replicated, the relative risk is often different in the different populations.

So it is very interesting and kind of a cutting edge science, but is it really that relevant to health care? You can come up with examples that can be very compelling. Because of, maybe, a smaller risk you look at people more closely and then you find something. But very often in medicine, and we know from the CT scans, you find little things and then you look and look and look, and the person goes through a lot of procedures, and there was nothing to begin with. They go through a lot of unnecessary procedures. Overall, there may not be a positive balance.

This information that you all put on the websites is for a person's informational use only. It is very disclaimed in the deCODEme site and any of the other sites that it is only for your own information and this should not delay anything you are going to do with your doctor or interfere with anything you are going to do with your doctor.

So, is this really ready for consumer-based health care, and do people understand the difference between provision of information and actually what is important for their medical care?

DR. GULCHER: You hit a lot of points there. When you talk about the validation and the replication, I think most of our companies are putting things on that have been widely replicated. We are not just talking about "Why do you say that?"

Take the atrial fibrillation genes. There are 12 different populations now where those have been replicated, just to take one example. That is not just us discovering these. In the first publication that we published we had to replicate in four other populations, and then since then other groups have independently done it.

The point is, they have already been replicated in multiple independent populations, which is the new standard for publication in some of those journals.

So I can't speak to microarray data, but at least in human genetics Dr. Collins and others have set standards, or suggested standards, that finally the

editors are abiding by for replication, because of that major problem that you brought up.

When it comes to what is the relative risk level that needs to be achieved to be clinically useful, that is really up to the physicians themselves. By the way, we are not saying that this is just personalized information that is just for recreation. We emphasize in every other paragraph that you should talk to your physician about this information. All the companies do offer genetic counselors, so clearly we are not just doing this for recreational purposes.

But the disclaimers are this is not a diagnostic. This does not mean you are going to get atrial fibrillation. It is a risk diagnostic. People need to be aware of that. Consumers need to be aware of that, and physicians as well. They are not determinative. That is why you see all that language that says this is not a diagnostic, it is a risk diagnostic or a risk genetic test, or whatever you want to call it.

When it comes to relative risk, at what level do you achieve a particular threshold for one of the

guidelines? Take breast cancer, for example. The late-onset form. Let's not talk about the early-onset form. The late-onset form of breast cancer. When you have a lifetime risk of 20 percent or greater the ACS has suggested that you do MRI screening in addition to mammography. That is a risk that is defined not specific to treatment. It is simply a lifetime risk. This is one of the additional risk factors that can contribute to lifetime risk beyond just family history.

So I think we are feeding into risk, which then feeds into established professional guidelines.

DR. LICINIO: I would like to just say something. Trust me, I am as much for this type of information as a person can be. I'm not using this to attack the area. But the website says the genetic product is for informational purposes only. It is not medical advice and it is not a substitute for professional medical advice, genetic counseling, diagnosis, or treatment. You must seek the advice of your physician or other qualified health provider with any questions you may have regarding the genetic aspects of a medical matter, and you must not disregard

professional medical advice or delay in seeking it because of the results of a genetic scan or anything you have read on the deCODEme site.

The website also states that deCODEme is an anonymous information service. It is not a medical service, not a genetic test, and it is not designed for medical decision-making. Therefore, it is not covered by health insurance companies.

That is what I find a little confusing.

DR. GULCHER: It is not reimbursed, certainly. It is not a substitute for your physician or a genetic counselor. A lot of those are self-evident things. But it is very important to inform the consumer that we are not making a diagnosis for them.

Just because they are at lower risk of atrial fibrillation and they have palpitations or have a stroke, that doesn't mean that they should not be evaluated for atrial fibrillation. I think that is the major point.

DR. KHOURY: First, thank you. This is a wonderful beginning of conversation. I want to quote something that Kari Stefansson said in April in one of the newspapers. He said that "Every college-educated

person in the U.S. should have this test within the next five years. We cannot afford not to." That seems to be a little bit different from the kind of thinking we are talking about here.

But the idea behind all of this is that I think this information is not ready for primetime. I think part of the problem is the concept of lost in translation. When you talk about validation, you mean replication. When I talk about clinical validity, that is a very different concept. It is the ability to predict the health outcomes that we are trying to predict here, whether it is risk factors or diagnostic tests, predictive value, clinical sensitivity or specificity.

When you talk about value to consumers, I talk about clinical utility, I talk about the balance of harms and benefits. In order to do that, we need research. When I heard Linda just talk now, I thought she was a research enterprise, not somebody who is selling me a test for a thousand bucks.

That is the kind of stuff we need to do. We need to figure out what this information means for clinical validity and how it is going to improve health

outcomes without providing harms.

Your own personal example is a powerful anecdote. It is a hypothesis-generating anecdote. It doesn't prove clinical utility. It means that we need a clinical trial to show whether we follow up a hundred people like you or not, whether the deployment of a prostate cancer-specific test would do more good than harm on a population level.

I think we have a problem in lost in translation. We need to get together to speak the same language of what we mean by clinical validity and utility. In order to do that, I think the dialogue has just begun.

So, no question for me. Thank you.

MS. AVEY: I would just comment to Muin that that is exactly why we wanted to start this company. I think this year has been different than what I was experiencing when I was with Perlagen where we just couldn't find cohorts large enough to study. It was so hard. We went to multiple centers. You would have to do a consortium self-study. Then you would have different diagnostic criteria used in each one, so you never quite

knew do we really have the same phenotype in all these groups.

[We need] to have a centralized way to collect all of this information. Eventually, if people are willing through maybe Cleveland Clinic, who has now partnered with Google Health, we can start pulling in this phenotypic information through a health record that is very standardized across many, many people and across many different, diverse groups. We are really hoping that merging that now with genetic information in a Web 2.0 environment is going to be very powerful. That is the goal, but we need to work with all the organizations to make it happen.

MS. AU: We have Rochelle, Marc, Mara, Jim, Kevin, Paul Miller, Mike, Gurvaneet, and Francis on the list. So, Rochelle.

DR. DREYFUSS: I think my question is short and I think it is mainly aimed at George. It is back to the question of costs. I'm curious whether you are affected by patents on any of the things that you are investigating. When you do the whole genome sequence I assume you go through the BRCA gene alleles as well. How

much does the cost of licensing add to the total cost?

DR. CHURCH: I think the effects of patents are certainly there, not so much in the instrumentation yet. I think some of the chip manufacturers have stayed away from certain IP issues. It has been somewhat limiting. Hopefully we will be able to get this straightened out. Maybe one of the other panelists can [speak to this.]

DR. DREYFUSS: How about on the sequences themselves?

DR. CHURCH: I think that is the only place where I see any limitations [unless] a large screen of the whole genome results in you going and getting a confirmed, CLIA-approved test on a very specific allele.

For example, if you did a PGP or 23andMe and then it went to Ryan's DNA Direct to get a myriad BRCA1 test, that would not be threatening because that would actually increase their market. I have talked to them about that, and they seem to be comfortable with it right now.

So far I don't see it as a huge barrier, and there is certainly an incentive to develop sequences and technology that is presented by the patent process which

I think is very positive. It could become a problem, but it isn't right now.

MS. AU: Marc, are you there?

DR. WILLIAMS: Yes, I'm here. I wish I could say I was on top of Ensign Peak because I have been there and it is a wonderful place to look out and think.

A couple of comments and then one question. The first one is that we have been talking a lot about new knowledge and the research. Muin very nicely summarized that point. I think the issue that I would raise is that the model that we are looking at here is really the potential of funding research on the issues of how important these things are using clinical revenue.

That is certainly not something new. We have danced around this before. But I think we at least need to be honest about the fact that we are looking at non-traditional research funding mechanisms to be able to learn about things that we don't currently know about, and some of that is now coming directly from the consumer. I think that we just need to be up front about that.

The second point is that there have been

comments made in the presentations and in the responses to the questions that risk information is linking to establish professional guidelines. While that is true, I think we have to realize that what we are talking about here is clinical plausibility, not validity or utility in the sense of really understanding that there is an evidence base that suggests that this genetic information that is associated with other risk factors, family history, environment, et cetera, in fact does impact risk and in fact does argue for different modalities.

We can say that we think if we got people on Warfarin because of their genetic risk for atrial fibrillation that that would save a billion dollars a year for the healthcare system. That is all well and good, but it is completely assumption-based.

The reality is, if we put a lot of people on Warfarin and it doesn't work, we are going to add cost to the system related to the complications of using a medication that, even if we used pharmacogenomic information to better dose it, is still going to result in people with thrombosis and bleeding.

So I have a question, and I apologize that,

because I haven't been able to log into the Webcast, I'm not sure exactly who I'm directing it to. But it was the presenter that gave the personal anecdote relating to prostate cancer. Because it is a personal question, I think you can fairly say "I don't want to answer it."

But you mentioned in your presentation that you brought this information to your primary care physician, who then acted on the information. The question I have is, how much education did you need to do as an informed consumer to teach your primary care physician what to do? Because I would hold that it would be extraordinarily unusual that your primary care physician was in fact positioned to be able to use that information.

DR. GULCHER: Before I answer that personal question, I did mention in the talk yesterday that we have a preventive cardiologist that recommends some of these individual tests for MI and type II diabetes in his preventive cardiology practice. For some patients he even recommends that they get deCODEme for all that, primarily for him to assess the cardiovascular aspects.

So he has a patient who comes in with a PSA of three whom he had been evaluating for other risk factors.

He said, go to your urologist. I don't know anything beyond the heart. Most cardiologists will freely admit that, and they are proud of it.

But he goes to the urologist, who says, "I'm not going to do anything. You are 55 years old. You are in the normal range."

But then he gets his deCODEme report later and his cardiologist says, "Well, you don't see any increased risk for cardiovascular, but what about this prostate cancer?" He sends him back to the urologist, and the urologist goes ahead and does the ultrasound-guided biopsy. He has even more cancer and a higher grade than I have.

Once again, another anecdotal example, but here is an example where it is an incidental finding by a cardiologist who has no business thinking about cancer. But yet, it probably led to some useful intervention, which represents how, really, things should be if we could move from intervention to prevention.

So from my own personal experience, I did have to show him the descriptions of what we put on our reports. As I showed you in one of my slides, we try to

make it simple for the physician, emphasize these are risk factors, these are not Mendelian, determinative genetic factors. We give them a risk. We describe the bottom line stuff at the top. We give them the more detailed part of the bottom.

But we convert that into a lifetime risk. We show the assumptions of what we think the baseline risk is, and the big differences among the three companies actually are more on that, which we are simply quoting some contradictory literature out there in epidemiologic studies. But the relative risks themselves in some cases will lead to more intensive intervention. In other cases it will just be done the standard way, which is ignore the PSA.

So I did have to show him some of the reports and whatever, but I did not put a gun to his head to suggest that he send me to a urologist.

MS. AU: Mara.

MS. ASPINALL: Thank you. Let me first start by saying thank you all for your openness and transparency today and yesterday, and being willing to very freely be a part of this and engage in this

discussion. I do think that this is, as is personalized health care, an industry in its adolescence. It is only through these types of discussions that we can get into adulthood, whatever that looks like.

I want to go back a little bit to I think it was about 18 months ago when the Secretary and HHS issued their report on personalized health care. It combined personalized medicine with the IT arena. The Secretary mentioned it today in terms of the electronic medical record. A lot of what you all are talking about is both a healthcare company but fundamentally an IT company, a data-oriented company, that is focused on providing information.

So, two questions related to that. The first one is the fundamental one that hasn't come up yet. [Using] David's example from this morning, how do you reconcile the different results he got from different areas?

One of the biggest challenges that we have in diagnostics, and perceived probably throughout the healthcare environment but particularly scrutinized right now in diagnostics, is getting different results from

different labs and ensuring that does not happen. So HER2 testing standards and ensuring that it doesn't matter what lab you go to, if you are getting the same test you will get the same result.

I will add I think critical for the respect and the recognition of the key role diagnostics play is a fundamental confidence in the system itself. It relates back to what this Committee did in terms of having standards and having regulations to ensure that a physician can choose and a consumer can choose to do the test or not, but to believe that no matter who they get it to is a reputable lab or a reputable genomics company and they will get the same result.

So my first question is how you reconcile David's experience and how important is that. I know you have talked about some industry-wide initiatives, but I would like to hear more about that.

Then, secondly, how does it relate to the electronic medical record. Does the consumer need to hold that and, five years later, remember that it happened? Are the healthcare systems, not individual physicians but the systems, ready to take this data so

when you get a test five years from now you can get your metabolism score and say -- and I don't know if you all do metabolism -- "I don't want to prescribe this at this dose because the system gives me a clue that says we have to do it differently"? Or, is that burden today on the consumer?

It is those two pieces but very much, I think, related to the issue of data and validity of the data.

DR. GULCHER: Just to be clear, when David Duncan was going through his results, whatever overlap there was in terms of the actual testing of what he called the raw genetic data, there was no discrepancy, at least with respect to the three services. Is that right, David? The actual genotype calls. Did you find any errors among the three companies? Were there any errors?

MR. DUNCAN: No.

DR. GULCHER: No differences.

I'm just putting that out there. We seem to be able to measure things correctly. Now the question is can we actually annotate them correctly.

There are different ways of converting from odds ratio to relative risk. Dietrich does it

differently than we do it, a little bit. In some cases that leads to a different result. In many cases it doesn't matter. He thinks of the control populations as being super controls, I think, and we think of it as being more population controls in terms of our own studies and other things.

We will get together on that. We have been brought together by Ed from the PMC, and I think we can agree, especially with some of your input, on what those standards should be in terms of annotation and combining the markers together. I think we would welcome that feedback. I think that would give greater clarity, with or without a Good Housekeeping Stamp of Approval. I think that would certainly go a long way to addressing that because I think that is the vast majority of the variation among what you saw in terms of the annotations.

DR. TEUTSCH: We are going to need to wrap this up very soon, so I ask the next few folks to ask very succinct questions, and I'm looking for very succinct responses.

MS. AU: Can I just follow up? Electronic medical records, are they integrated? Are the systems

ready to do that?

MS. AVEY: I think, at least the way we are envisioning it, that we will look to companies like Google and Microsoft, who are doing the heavy lifting of merging or creating PHRs that will sit on top of the MRs. They have already announced partnerships. I think Kaiser is working with Microsoft and Cleveland Clinic has announced an arrangement with Google. They will become the standard of an individual. If they say "I want my PHR. I want my own personal health record," they would be able to draw that up through their clinical center if there is a partnership there.

Then they are also working with places like Long's and Walgreen's. You can pull up all your prescription information as well and store it in one place where you control it.

We don't think genetic data itself makes sense to transfer into a PHR. It is more about what is a report that could sit on top of that data that would be easily transferable into that record. Then the patient would have the decision to say "I want to port this back over to my doctor."

We envision someday a two-way communication going on from genetic information to PHR to EMR. Something like that we think is pretty workable, but obviously it is very much in the early stages.

MS. AU: I'm sorry. We are just going to take two more questions, one from Paul and one from Francis, because he gets the honor of asking questions.

[Laughter.]

DR. MILLER: I don't know why I'm getting to ask a question.

I want to briefly go back to this research enterprise aspect because I'm really interested in that and particularly, Linda, your focus on that. How you communicate information with your customers I think is interesting, and your next steps that you are trying to do.

My question is, because you are communicating this kind of information and doing these studies through your database, are you subjected to federal human subjects regulations? Do you have IRBs and informed consents, and should you? Or is it simply we are going to look at your data and then we will send you an Email

back and tell you what we found. How does that play out?

MS. AVEY: Luckily, when I was at Perlagen I had to manage all of the OHRP work that we did and all of the oversight that we had as a company, so I was very familiar with IRBs. I had to go crack the whip to get all the scientists to go through the training. I went through the training.

We have implemented the same thing at 23andMe, where we have all of our scientists going through OHRP training. We have it all put away in a booklet. Everybody has to do that before they can even look at any customer's data, which is all de-identified. They don't have any means to really find out who these people really are.

We have talked to an IRB. We do have a consent form, so all of our customers do go through this consent, whether or not they read it. With some of the stuff, we bullet it out and put it in bigger letters so they read the really important parts that we think they should see.

We have talked to a commercial IRB, and this is a new model for them, just like for you and for the world. They need to really sit and think about it.

Because we don't have a protocol necessarily that is well defined, it is hard for them to get their heads around what exactly we are doing.

But it is going to be an ongoing discussion like we have with you, and we are eager to see if we can move that along. We have every intention of doing that. George can comment on how long it took him to get his consent form through the IRBs that he has worked with.

DR. CHURCH: It was one year to get the initial IRB in and 3.5 years to get the scaled-up version. I think that is reasonable considering the changes going on here.

MS. AU: Francis gets the last question.

DR. COLLINS: Thank you for that great opportunity.

[Laughter.]

DR. COLLINS: It will be quick. It follows up on a comment that Jeff made in his presentation and then came up already in the discussion. By the way, this has been a very useful panel. Thank you all for coming and talking about what your own plans, hopes, and dreams are.

Jeff, the thing I'm concerned about with regard

to the follow-up of findings is not only a circumstance where you have to educate the healthcare provider to take action but the concern where the healthcare provider takes unnecessary actions on the basis of not quite knowing what this means, perhaps having some trouble understanding risk factors in a quantitative sense, and as always, worrying about possible litigation if they don't then order every possible test.

In addition to your two anecdotes, one of them being yourself, where a prostate cancer genetic test resulted in some valuable information, one worries about how many other biopsies got done that were really not indicated on people whose PSA was very low, whose relative risk factor was quite small, and whose family history may have been negative, and who may have been 42 years old at the time.

To what extent, in your own thinking about how this all plays out as either a benefit or a risk to the public, is this an issue that there is going to be a tendency to follow up on modest risks by ordering more tests? I'm a physician, so I can say denigrating things about physicians, I guess, and denigrate myself at the

same time. Oftentimes physicians, without being quite sure what to do, just figure, "Well, we had better look into it."

My professor in medical school way back when said all non-indicated tests will be abnormal.

[Laughter.]

DR. COLLINS: That is often said but a true story. Then you have to do more tests to follow up on that.

So, what are your thoughts about that specifically, Jeff, since you have gone into a very specific example?

DR. GULCHER: Right. I think that is why we try to emphasize these are clinical risk factors like other clinical risk factors. Family history is a clinical risk factor. Environment, other conventional cardiovascular risk factors, or whatever. Physicians are using them on the basis of what are those risks conferring to their particular patient in the context of the general population risk.

That is why we try to convert these to relative risks and emphasize if it has been demonstrated that

these risk factors are indeed independent of other cardiovascular risk factors, the conventional ones, and independent of CRP and LPPLA2 and LPa, which has also been demonstrated in a cohort for cardiovascular markers.

If that is the case, you can do what physicians have been doing for a century: multiply independent risk factors together to define a composite risk. Then you act on that.

If that, for example, converts an intermediate risk patient based on ATP3 criteria and you multiply it by a risk factor of 1.3, if you are homozygous for 9P, some patients are going to get bumped up into the high-risk category. The LDL cholesterol level may be chosen by their physician, not by us but by their physician, to perhaps be at a lower level, 100 milligrams per deciliter instead of 130 milligrams per deciliter. That is one example of where it can potentially modify the risk factors up or down.

We are not saying that you are acting only on this genetic test. You are acting on that genetic test in the context of the other risk factors because this is just another clinical risk factor test.

DR. COLLINS: That would be true if every physician was thinking in exactly this kind of quantitative way. I guess what I'm wondering about is to what extent do you or do the other companies feel the responsibility to try to help physicians in that circumstance not overreact, even as you are promoting, of course, the value of this information. We all understand why you need to do that. How do you do so in such a way that doesn't cause healthcare providers to somehow attach even greater significance to these findings than they should and therefore to carry out a whole bunch of follow-up tests that are actually unnecessary?

DR. GULCHER: So you are concerned that a physician might act on a relative risk of 1.1, for example just because he says it is a little bit bigger.

DR. COLLINS: Yes.

DR. GULCHER: I think you are exactly right. We try to lead people through these risks and put it in context of other risk factors in our reports, but we don't come out and say "Don't do anything for this patient who has a relative risk of 1.1" because he may have other risk factors. The whole point is to emphasize

combining this information to the other information that you are already routinely collecting on those patients. It is the sum total of that composite risk that I presume in many cases, not all cases, is guiding physicians in their practice.

I mean most physicians. I disagree with whoever mentioned that most physicians aren't using Framingham. They are using a Framingham score and using the ATP3 criteria to risk stratify. These primary care physicians are doing so.

I think it fits well into a paradigm that already exists. We are already using family history for common disease like prostate cancer and breast cancer. It is totally analogous to that but independent of family history.

DR. TEUTSCH: We need to wrap up the session. I would like to thank the panel and everyone for engaging in a very lively and open discussion.

As all of you are aware, we are running a bit behind.

[Laughter.]

DR. TEUTSCH: Which is fine because we have had

good discussion this morning. We appreciate the extras that got added onto our schedule.

Just so you know, what we are going to do is we are going to hear from Kathy Hudson and then we are going to have a break for lunch. We are going to roll the discussion that we planned to have just among the Committee into the discussion on the priorities this afternoon with Paul.

Let us give a round of applause to all of our fine panelists.

[Applause.]

DR. TEUTSCH: The public comment period will begin right after lunch. I expect that will be around 1:25 to 1:30. I apologize to all of you. Hopefully you can all stay so we can be the beneficiaries of your thoughts.

MS. AU: Our next presenter is a frequent visitor to SACGHS, Dr. Kathy Hudson. She is the founder and director of the Genetics and Public Policy Center, located in Washington, D.C. Dr. Hudson's presentation will explore the public policy considerations for this emerging field of direct-to-consumer personal genome

services.

As soon as we get her talk cued up on the screen, she will drive us through this.

Public Policy Issues Surrounding Personalized Genome Services

Kathy Hudson, Ph.D.

[PowerPoint presentation.]

DR. HUDSON: I want to thank you for inviting me. I recognize that many of you are probably suffering from low blood sugar, and so snack carts will be coming through the aisles. Snack boxes are available for $5, wine and beer for $3.

[Laughter.]

DR. HUDSON: What I would like to do in the next 15 minutes -- I will go as quickly as I can -- is to put a little context around what you have heard already today. I will talk explicitly about some of the tensions that have been coming up recurrently over the course of the last day and a half. Then I will talk about some of the critical policy issues that I think we are facing today.

The whole genome association studies and the

kinds of companies that we heard from today really fall at the end of an evolutionary continuum in the kinds of tests that have been available directly to consumers over the last decade or so. Of course, the focus that we have heard today has been on health-related genetic testing. Beyond looking at SNPs, we can sequence entire genomes, as we heard from George earlier today.

The companies that we heard from are really only a subset of the companies that are offering health-related testing services in this space. This is a now outdated slide. We have a more updated version available now, I think, on our website where we categorize the companies in terms of what kinds of tests they are offering and focusing mostly, again, on health-related testing.

So, how do we look at this new paradigm in genetics. I think what we have heard recurrently and what we read about in the newspapers and in the medical journals is sort of this tension between the old precepts of genetic medicine and this new concept of personalized genomics. I want to go through these precepts really quickly because I think they are important in what we

have been hearing over and over again as some of the key stress points.

The first is that genetic testing requires pre- and post-test genetic counseling. The second is that you need a healthcare provider in all genetic testing. In the olden days genetic tests for non-actionable conditions were considered the highest risk. So when the predecessor to this Committee put tests into categories of what was most high risk and therefore warranted the highest degree of oversight, it was highly penetrant tests for which there was no intervention available. I think we actually might flip that today. And, that genetic information is special.

I think we can challenge all of these precepts today. First of all, in terms of pre- and post-test genetic counseling, there are too many genes, not enough genetic counselors, it is too expensive, and a model that was really built on reproductive genetic testing and Huntington's disease may not fit with the kind of testing that is available today.

In the olden days we had odds ratios of greater than five and they were extremely rare. Today we have

these teeny tiny odds ratios and they are proliferating like crazy.

The second precept, no testing without a healthcare provider as an intermediary. As Ryan mentioned earlier, not all genetic tests are created equal. They pose different risks for interpretation and for intervention. It may not be a viable model given high levels of consumer interest. There are inconsistent state laws, and I will come back to this, about who can offer a genetic test.

Third, about actionable or non-actionable information, we have heard a reference to the Reveal Study in which results were provided back to people about their Alzheimer's risks and in fact there was no demonstrable increase in anxiety, jumping off of bridges, et cetera. So people can handle this information where even there is nothing they can do about it.

In fact, I think we really need to focus our attention on the validity of tests where there is something you can do about it. If you are going to take a drug or not take a drug, have surgery or not have surgery, the validity of those tests is of utmost

importance.

Lastly, genetic information as being special. I think we in genetics of course think genetics is special, but we worry that the public thinks it is special, genetic exceptionalism or determinism. I think that while that may have been at one point true among the general public it is no longer true. When we did a survey recently of nearly 5,000 people and asked about genetic information versus risk information, generic information, there were no discernible differences between people's appetite for that information and concerns about that information.

In the old days we had this very systematic way of translating genomics or translating biomedical research into health impacts, and now we are leapfrogging over some of those essential steps, or what we used to view as essential steps. We are in the midst of a wave of creative destruction which is making many of us uncomfortable.

So, what should our response be. We could get our genomes done, and some of us may have done that. We could start our own company, although we may be a little

late.

[Laughter.]

DR. HUDSON: And as someone said yesterday, you have to be blond.

We could ignore the companies. As one well-known genomicist said, they are just a nuisance. We could insult them, and that has certainly been done in some quarters. Or we could support needed policy changes.

We have heard a lot about the promise of DTC genomic and genetic testing. I won't go through that. I want to focus a little bit on some of the concerns that have been expressed about DTC genomic and genetic testing, about consumers not being able to understand it, about consumers being especially vulnerable, about consumers getting tested without thinking about their family members, and forgoing standard treatments or getting unnecessary treatments, as Francis brought up in the last panel discussion.

The essential point I want to make here is that this is all knowable information. Instead of speculating about this, this is knowable information and we should be

supporting studies to actually get this information.

On the more policy side of the equation, there are concerns about the adequacy of privacy protections, about the validity of the tests, about the competency of the laboratories, about the evidence to support the claims that are being made, about the protection for research participants, and actually, an issue that I don't think has come yet in this meeting. With DTC testing especially with buckle swabs where you are sending it off and there is no person in front of you, there is a possibility for surreptitious testing of somebody without their permission.

This Committee knows well that there are enormous gaps in the oversight of the quality of genetic tests and has made some really fantastic recommendations in terms of policy actions that are now before the Secretary. I won't go over those because those are very familiar to you.

I will point out on the slide that I mentioned that there is no HHS authority over false claims being made by companies. There has been no FTC enforcement action, although I do understand that there are now some

investigations underway. That is an interesting new development.

An additional problem that we have in terms of oversight of genetic testing is some lack of clarity in terms of who is authorized or should be authorized to order and interpret tests, the limited applicability of HIPAA, and the limited applicability of the Common Rule for Protection of Research Subjects.

I will spend just a second now talking about protection of research subjects. In the late '70s we put in place the Common Rule for the Protection of Human Research Subjects. That was really based on principles of beneficence, justice, and respect for persons. We may need to go back and reevaluate whether or not a model that was somewhat paternalistic and protective of physical harms really fits in today's biomedical research context.

But it is important to note that the common rule does not necessarily extend to all research that we would care about, including some that is being conducted by DTC companies.

Outside of the federal government, which I

believe plays a very important role, especially in quality and in making sure that claims are consistent with the evidence, there is certainly an opportunity for professional groups and industry to develop guidelines. Those have the advantages of being flexible and those groups having the right expertise, although they may have some internal conflict of interest. Those guidelines would be voluntary. That means that not everybody has to participate and abide by the rules.

There have been a number of professional statements. I'm particularly fond of this one, since I was involved in its creation, from the American Society of Human Genetics which really says that some tests are appropriate for being offered directly to consumers but we need to make sure that the tests are accurate and reliable and that the claims that are made about them are also accurate.

ACMG, a few months ago, took a different position and recommended that healthcare providers be involved in ordering and interpreting all genetic tests. This was basically putting a stake in the ground, saying we, the medical geneticist community, need to be involved

in this testing.

More recently still, the American Medical Association actually provided an interesting recommendation and provided some interesting clarification, I think, about what does it mean to have a doctor involved. The AMA recommended that states restrict the performance of clinical and laboratory genetic testing to individuals under the personal supervision of a healthcare professional. That is not somebody you have talked to that has signed off on your requisition. It is somebody who is actually overseeing your care.

The states have always had a role in laboratory testing and have recently made the entire scenery more interesting. They administer the Clinical Laboratory Improvement Acts, and they can impose higher standards than CLIA requires, such as New York. Ann Willey is here from New York. The states [also] determine who is an authorized person to order and receive laboratory tests.

This is an evaluation that we did some time ago on the state laws regarding who is an authorized person. The dark purple states are those where an authorized

person is usually not defined, which means everybody is an authorized person. [That] means I'm an authorized person, so I can order my own clinical laboratory testing.

Lavender is limited, and you will notice that California and New York are both limited. I will come back to that. In the whitish, DTC is not permitted at all. A healthcare provider must be involved.

Where DTC is permitted, as I mentioned, the state laws are usually silent on the issue. Where DTC is not permitted, and one example is Georgia, they are very clear that it has to be a licensed healthcare provider who is authorized by law to use the findings. So I as a consumer am not authorized by law to use the findings.

Then there are the mixed states. Both California and New York fall into this category. This is an excerpt from the California statute. There are prohibitions with exceptions, and it is the exceptions that put it into the limited allowance.

In the absence of federal leadership in a number of areas in genetic testing, particularly oversight of quality, the states have stepped in. We

have seen headline after headline after headline about the states trying to step in and protect their citizens.

What are the policy options as we move forward. We could take the stance that is a buyer beware marketplace and consumers should be informed about what to take into consideration as they consider buying these testing services. We could demand transparency, as was embedded in the Oversight Report in terms of a genetic testing registry which would include information and evidence that supports the test, how it is performed, and its characteristics. We could require third party review.

We could be taking action against false claims. I believe that we could do that both at the federal and state level and perhaps in a voluntary way outside of government.

We might want to think about creating a category of laboratory-developed tests that would be the moral equivalent of over-the-counter drugs. If we can now go into the drugstore, and we know what we have, and buy that drug over the counter without a physician, aren't there also tests that should be similarly

accessible to us without having to make an appointment, go see the doctor, and by the time you have actually gotten to the doctor and taken time off work the thing is resolved. I think we might want to think about this as a new mechanism.

HIPAA. People within the Beltway know what a HIPAA-covered entity is, which is sort of pathetic.

[Laughter.]

DR. HUDSON: Companies that do not bill electronically are not HIPAA-covered entities. So, at least federally afforded and state-enforced privacy protections usually don't go with the information. I think these companies, particularly 23andMe, selling a service at the same time that they are conducting research raise interesting and provocative issues about what we need to do to protect research subjects or research participants in this new age of personalized genomics.

That was really speedy. Now we can hopefully go to lunch pretty quickly. I want to thank my funder, the Pew Charitable Trust.

[Applause.]

Question-and-Answer Session

MS. AU: Because Dr. Hudson was so speedy, we can take one or two questions. Kevin.

DR. FITZGERALD: You have to have quick hands around here.

[Laughter.]

DR. FITZGERALD: Thank you, Kathy. Again, as always, very thought-provoking, so I have a question. You mentioned in the statement that you were one of the authors of that safety should come first. You also mentioned that there is a great deal of evidence we need to have in order to make decisions that we don't yet have. Is it then logical to conclude that much of what is going on now you think shouldn't be going on because we don't have the evidence to decide what is safe and what isn't?

DR. HUDSON: I think it is hard to know. The actual answer is it is hard to know. If you look at some tests that are being offered, you can't tell what the gene is, you can't tell what the variant is, you can't find any publications. In some cases, the disorder that is being tested for doesn't exist in the scientific

literature. It is just very difficult to know because we are not demanding the kind of transparency that we really need.

DR. FITZGERALD: Right. If you are saying safety first and we don't know, does that mean don't do anything?

DR. HUDSON: There are a couple of interesting models. One is, we could put in place this genetic testing registry tomorrow. It is not that complicated. I think we need to move ahead expeditiously with putting that in place.

Secondly, I think that we could have tests on the market where we either haven't had a chance to evaluate them or we don't yet quite have all the evidence and collect evidence as we go forward. It is approval with additional evidence collection.

There are ways where we could address the pursuit of the perfect not denying us some of the good tests that are available out there.

I should say there is a whole slew of tests that have been out in clinical practice and validated for a very long time that we need to figure out some

mechanism of just grandfathering those in. We know what they do, we know how they behave, and we know the molecular biology and cell biology underlying them.

MS. AU: Thank you, Dr. Hudson. I'm sure we will see you back here again.

[Laughter.]

MS. AU: Back to Steve.

DR. TEUTSCH: Great. Thanks, Kathy. Thanks, Sylvia, to you for organizing this session.

[Applause.]

DR. TEUTSCH: Obviously, a stimulating and important area. We will be talking more about it later this afternoon.

For now, since you and Kathy graciously got us done by 10 to one, let's plan to meet back here at 1:20. We will have a half hour. There is a cafeteria down the hall for those of you who don't have a boxed lunch. Then we will take up the public comments. Thanks, all.

[Lunch recess taken at 12:54 p.m.]

AFTERNOON SESSION

[Reconvened at 1:32 p.m.]

Public Comments

DR. TEUTSCH: Good afternoon. We have come to the public comment part of our meeting. This is, as all of you know, one of the critical things that we do at every meeting. The Committee uses this as an opportunity to obtain input from the public and get their suggestions so that they can inform our deliberations on a wide variety of health and societal issues.

We, as always, greatly value the input that we get from the public. As you can see from our earlier discussion yesterday, we received an enormous number of comments which were extremely helpful in shaping our priorities, so we will get back to that.

We have four individuals who have indicated that they plan to speak. We will take them one at a time. Each of them will be speaking for five minutes. We very much appreciate all of your thoughts and input, and I think we have copies of your full statements which will be made part of the meeting record.

Let's start with Michele Schoonmaker, who is

the director of government affairs of Cepheid and representing the Association for Molecular Pathology. Michele, we have appreciated your input in the past and look forward to your comments.

Comments by Michele Schoonmaker, Ph.D.

On Behalf of the Association for Molecular Pathology

DR. SCHOONMAKER: Great. Thank you. Good afternoon, Mr. Chairman and members of the Committee. Thank you for the opportunity to speak with you. I am Michele Schoonmaker, representing the Association for Molecular Pathology.

AMP is an international medical professional association representing approximately 1,500 physicians, doctoral scientists, and medical technologists who perform laboratory testing based on the knowledge derived from molecular biology, genetics, and genomics.

I will be providing comments on high priority areas of focus for consideration by the Committee in the coming year. My comments today will briefly summarize the more detailed written statement that we have submitted for your review.

AMP recommends that the following topics be

considered for Committee review with development of recommendations. First, we encourage the Committee to investigate the current mechanisms for funding outcomes research for clinical diagnostic tests. Specific areas to consider include implementation and performance of tests in clinical practice settings, the impact of the physician ordering practices and patient decision-making on test utilization, and the impact of test interpretation on patient management and family decision-making.

Second, coverage and reimbursement decisions are increasingly made based on the comparative effectiveness of various treatments. Genomic information may identify population subgroups that contradict aggregate population study findings and challenge population-based treatment decisions. The Committee should explore the role genomics will play in this emerging trend in health policy research.

Third, we recommend that the Committee survey the clinical decision support tools currently under development and explore future needs for the integration of genomic information into the clinical decision support

tools, including the development of standards and specific clinical services.

In addition, the Committee should evaluate the current oversight and policy needs to overcome systematic barriers and challenges for the integration of these tools into the patient care setting.

Fourth, we request that the Committee continue to examine the structure and consequences of non-traditional genetic testing. Important aspects include an understanding of how non-traditional genetic testing will be used by the lay public and an understanding of how these test results will be interfaced with traditional genetic medical practice.

The development of appropriate quality assurance measures and practices to validate the quality of non-traditional laboratory test results or integration of these laboratories into the current regulatory oversight is critical to the utilization of this information in conventional clinical evaluations and treatment decisions.

Finally, we request that the Committee continue monitoring oversight efforts in reimbursement and

coverage for genetic tests. SACGHS has released several influential and important reports on both of these issues, and we encourage continued efforts to work with stakeholders within and outside of HHS to implement your recommendations to improve the quality of genetic tests and to achieve appropriate reimbursements for providers of the genetic tests.

On behalf of AMP, I would like to thank the members of the Committee for their time and attention.

DR. TEUTSCH: Thank you, Michele. Any questions or comments for Michele?

[No response.]

DR. TEUTSCH: That is great. As you know, we take all those issues very seriously and look forward to seeing how we can help move some of those agendas forward. Thank you for your input.

DR. SCHOONMAKER: Great. Thanks.

DR. TEUTSCH: Our next presenter is Amy Miller. Great. Welcome. Amy is the public policy director for the Personalized Medicine Coalition. We look forward to what you have to say. Good afternoon.

Comments by Amy Miller, Ph.D.

Personalized Medicine Coalition

DR. A. MILLER: Thank you, Chair and members of the Committee. I am Amy Miller, public policy director for the Personalized Medicine Coalition. PMC represents all stakeholders in personalized medicine, from the academics who do the research to the medical institutions that put it into practice, to diagnostic companies, pharmaceutical companies, insurance companies, and we even have among our members ex officio government officials who work with us to make good policy happen.

We are a consensus-reaching organization. We don't vote. That gives us a unique place in the world of personalized medicine. Much like this group, we have all the stakeholders coming together to talk.

Although PMC has submitted to SACGHS where we think your priorities should go, what I wanted to talk today with you about was the space of consumer genomics. As a couple of the speakers have already mentioned, PMC met with the leading companies to discuss the possibility of working together towards standards of operation and basic guidelines about how these companies should act.

There are a number of issues that need to be discussed. We feel that we are at the very beginning of this conversation. Yesterday and today and the previous SACGHS meeting in particular have started to air a number of questions that go unanswered or that we need to have answered by all the different constituents in personalized medicine. PMC has agreed to work with the companies on convening the stakeholders in personalized medicine to talk about consumer genomics and to build on the work that HHS began yesterday and that this group is continuing today and move it forward, possibly.

We see the output of that effort as possibly being some basic guidelines for operating in this space. We see the possibility of a consumer guide in selecting these services, and we see the possibility of a physician education tool, be it as simple as a brochure or as complex as a report.

We are at the beginning, as I mentioned, of this conversation. We are also at the beginning of what PMC is looking to do in fostering this conversation and coming to a consensus around this issue. So, thank you.

Also, I should mention we will keep the SACGHS

apprised of what we are doing, of course.

DR. TEUTSCH: Thank you. Any comments or questions for Amy? I have a question for you. Since there is a clear interest on the part of advising the Secretary on these issues, how do you see what PMC is trying to do to integrate with the more public and governmental functions so that there is some common set of guidance?

DR. A. MILLER: PMC does have ex officio government people on our committees, so we do have representation in our organization. We will work with those members and possibly reach out to some other government members who don't often participate in the PMC process.

We will work with the Secretary's Personalized Healthcare Initiative to make sure that the work that began yesterday moves forward. We will revisit what is written in the report that you recently published and revisit this conversation to make sure that all the questions raised here today are part of our deliberations moving forward.

We are also open to, in answer to your

question, any government official as well.

DR. TEUTSCH: Mara.

MS. ASPINALL: I'm involved in the PMC, but it sounded like several of the panelists earlier talked about working with PMC and getting a number of groups together. Is it time to describe what that is and what role you anticipate that playing?

DR. A. MILLER: We are at the beginning of the conversation, actually, in terms of planning what we are thinking about doing. I think our goal is to bring together all the constituents around this issue and do a PMC-type event. What we have done in the past is issue a brief on a topic, convene everybody in a conference, talk about it, and then do some sort of post-meeting product. In this case, it could take a number of forms: a consumer education guide, an M.D. education guide, and guidance for the industry on operation.

But we are at the beginning of the conversation.

DR. TEUTSCH: Thank you very much.

DR. A. MILLER: Thank you for your time.

DR. TEUTSCH: We appreciate your suggestions.

Our next speaker is Rick Carlson. Rick, are you here? I didn't think I saw you. Is someone here representing Rick?

[No response.]

DR. TEUTSCH: Taking that as a no, then we will move on to another friend of the Committee, Ann Willey, who is the director of the Office of Laboratory Policy and Planning at the Wadsworth Center at the New York State Department of Health.

Comments by Ann Willey, Ph.D., J.D.

New York State Department of Health

DR. WILLEY: First, I want to thank the Committee for this opportunity. Some of what I'm going to say is known to the Committee but I wanted to put it in the context of speaking to the issue of these entities that are now marketing direct-to-consumer marketing and/or direct-to-consumer access of whole genome profiling of some kind, and the relation to the New York State regulatory program.

New York has been mentioned several times over the last couple of days, some of it correctly, some of it with some perhaps erroneous implications.

The New York State Clinical Laboratory Reference System has been responsible for the oversight of clinical laboratories performing analytical testing on specimens collected in the State of New York since 1964. The categories of testing covered are specified either in the enabling statute or in its implementing regulations.

The clinical laboratory permit requirements include personnel standards, credentialing of the laboratory director, physical facility inspection, proficiency testing, test authorization requirements and result reporting standards, and business practice requirements, among others.

Category-specific standards are stated in our regulations and/or in our interpretive standards, which are issued by the program. Standards for genetic testing related to cytogenetics were first added in 1972 for genetic testing, including biochemical genetics and molecular or DNA-based genetic testing in 1990. Other genomic types of testing, which might include nuclear DNA, RNA, or gene expression profiles, are also covered in other categories such as molecular oncology.

Key elements of the oversight of our genetic testing labs include the training and experience of the responsible laboratory director in the relevant areas of genetics and the performance of tests that are generally accepted in laboratory medicine -- these are tests which were in general use prior to 1976, clearly not those we are talking about today -- or approved by the FDA as cleared or approved in vitro diagnostic devices, also not the kinds of tests we are talking about today.

The only other alternative is that the assay must be approved by the department.

Since 1990 the department has reviewed all laboratory-developed genetic tests as to their analytical validity and clinical validity prior to their approval for addition to the test menu of any permitted lab.

Genetic testing based on a single genome sequence or gene product detection or multiplexed assays detecting multiple targets concurrently, including those used in the various genome profiles, are all subject to similar review standards.

The recent explosion of Internet marketing of various genetic profiling assays for individualized

genome information systems have raised new paradigms for patient or consumer access to such lab analysis. The Department routinely monitors the Internet for entities purporting to offer laboratory services of any kind. Lab services in our system are defined as the performance of an analytical analysis on specimens derived from the human body and the reporting of individualized results for almost any purpose.

We don't limit it to diagnosis of disease and health assessment. The measurement of any component in a biological specimen gets defined as a lab test.

All such entities that we identify on the Internet are routinely notified that in order to offer their services in New York the testing entity must seek and obtain a clinical laboratory permit from the Department and meet all relevant requirements and standards. Just as an aside, these requirements apply regardless of the physical location of that entity anywhere in the world. If they receive a specimen from the State of New York, they are subject to New York requirements.

We have sent 31 entities purporting to offer

some type of genetic testing services notices that they must seek permits in the last year. These letters indicate that in the absence of such a permit the service cannot be offered in New York. It is slightly different than the cease and desist type of letter that was sent by California.

That is 31 labs offering genetic tests. We send hundreds of these warning letters with the new age of the Internet.

I do have the list of the 31 entities with me. I thank Kathy Hudson for reminding us that the major entities we have heard from in the last two days are not the major problem in this arena. There are a huge number, and I'm going to go home and add two more tomorrow.

[Laughter.]

DR. WILLEY: There are more and more of these entities purporting to offer some kind of genomic profiling.

Unfortunately for the major players that we have been hearing from today, all of whom have indicated their full intent to comply with whatever requirements

and regulations that are put forth, there are many that have no intention of complying. The only way a regulatory program can make the distinction is by forcing all players through the same keyhole, if you will. It is a process that has some burden and delays and problems with it.

Although over 150 laboratories hold New York State permits for various genetic testing menus, none of the major entities marketing consumer access to genetic profiling or their contract laboratories currently hold New York State permits for that purpose.

The Department is in discussions with several of the entities that wish to offer these services in New York, and the issues under discussion include the requirement for the submission by the testing laboratory of the necessary assay descriptions, analytical validation data, and documentation of the clinical validity for the use of these genetic markers in advising the client about health issues. This may be the easiest issue to resolve, depending on the variety of marker to be tested and the known clinical associations for those markers.

The second item is the resolution of the business relationship between the marketing entity, the data management and interpretation process provider, and the testing laboratory. Within the constraints of New York law related to corporate practice of medicine, which is prohibited, direct billing requirements for laboratories -- the lab that does the test bills the patient -- and inducements, those between the laboratory and the ordering entity, there can be no inducement, no payment, no contractual arrangement between the individual requesting the test and the laboratory. These are complex and often circular issues and have not yet been easy to resolve.

The third item is the physician-patient relationship between the person authorized to order the test and the person tested, and the relationship of that provider with the marketing entity, the data management and interpretation entity, and the laboratory. Laboratories, under New York State permit, are prohibited from performing testing on New York residents except as requested by a person authorized by law to use those test results. For those kinds of tests, that is generally a

healthcare provider with an established provider-patient relationship with the tested individual.

The New York program views these genome profiling scenarios as no different than any other clinical laboratory genetic testing menu and expects the providers to comply with all applicable permit and business model requirements. We remain open to working with all interested providers of such services through the permitting process. Thank you.

DR. TEUTSCH: Thank you, Ann. Any comments or questions for Ann? Obviously a topic of considerable interest.

DR. FITZGERALD: Ann, just one quick clarification. Thanks again for updating us on things. So, is it the case that in New York right now there are no direct-to-consumer organizations that have made these arrangements yet with New York State? Did I hear you correctly?

DR. WILLEY: There are entities which market direct-to-consumer marketing that are not providing direct access testing. DNA Direct offers its services in New York. They are not a laboratory, but all of the

laboratories that they use for their monogenic gene, disease-specific testing for a New York resident must be New York-permitted, and they are.

But for genome profiling -- they all know it -- Navigenics, deCODE, and 23andMe do not yet hold permit. Some of their contract laboratories where that is the mode of testing have submitted. We haven't finished the review process for the analytical and clinical validity of the assays that they intend to include in those profiles.

But the biggest stumbling block at the moment are the business relationships between these intermediaries and the laboratory: who is collecting the money; who is paying the lab; who is providing the counseling; who is a physician; who is a counselor; what are all these relationships. That is the biggest stumbling block at the moment.

DR. FITZGERALD: Excellent. Thank you.

DR. TEUTSCH: Thank you, Ann. We will look forward to hearing how all of this proceeds in New York and in California.

Thanks to all of you. I think the Committee

should all have your comments in their folders. We appreciate all of the public input each time.

This afternoon we have two additional things. We are going to get, first, an update from Barbara Burns McGrath on the Education and Training Taskforce. I will turn it over to her, and then we will wrap up with a discussion on the priorities and the follow-up on this morning's discussion. Barbara.

We are scheduled until 2:05. If you can do by 2:10, it would be lovely. If you can.

DR. McGRATH: We will all watch the clock together.

Presentation of Proposed Action Plan of SACGHS Taskforce on Education and Training

Barbara Burns McGrath, R.N., Ph.D.

[PowerPoint presentation.]

DR. McGRATH: I'm going to be talking 10 or 15 minutes about the Education and Training Taskforce. We will show the membership in just a moment.

This is an issue that has resurfaced a lot in the last two days. Yesterday when we did our priority scanning, we did a little look and there were four topics

that explicitly listed genetics education and training of the work force that rose to the hot level on the scan, the 3.5 level and above. So it was very high on the priority list.

Yesterday afternoon and today the topic kept recircling on even the ones that didn't meet the 3.5 level yesterday. I was noticing there were other areas that were throughout the priority areas that I think also come under this rubric. One is consumer access to genomic information. Health disparities can be looked at through this lens. The electronic health record and personal health record, public health applications of genomics, and coverage and reimbursement all have aspects that I think have some attachment to the notion of genetics education and training.

In yesterday afternoon's session and this morning that issue came up a lot again, and it got to have a sense that whatever the question was where there was a particular dilemma the answer was better training for professionals and consumers was the answer to it.

I think this topic was one that was identified with the first SAC group when it was originally formed in

2002, I think it was. It has resurfaced now, and I don't think it is going to go away. I think we are ready to roll up our sleeves and work on this one.

These are the committee members. There are going to be a few changes, but basically that is who has been working on it so far. We are always looking for more members, so if you are intrigued, contact us.

Today's purpose is to talk about two pieces of information we have, and these are under Tab 5 in your booklet. [We will] go over the revised taskforce charge that we worked on last time. We will talk about our activities, and we will present the draft action plan. The goal for today is to reach a consensus on both of those documents, the taskforce charge and the action plan.

As a quick update, at the last meeting there was a discussion and it was suggested that we narrow the scope of stakeholders. The original list was pretty long and broad. We were asked to consider various education mechanisms and modalities to be more creative than just thinking about post baccalaureate training or whatever, to focus on issues specific to genetics and actionable by

HHS, to narrow it not to things like health literacy but to issues around genetics and things where the federal government has a role to play, and of course, aim for actionable outcomes.

I'm going to read the draft charge. As I said, it is on Tab 5. I will read it fairly quickly. This is asking for your approval on the wording on this. We can talk about all of this at the end of this session so we know we have time.

This is the draft charge: "Advances in genetics and genomics are leading to a better understanding of disease processes and improved application of genetic testing to guide health decisions. With increased integration of genetics into other medical disciplines however, health professionals with or without training or expertise in genetics are challenged to keep pace with this dynamic and rapidly evolving field. Education will have to address the growing importance of genetics in common diseases, which likely will require more knowledge and understanding about risk assessment and communication. In addition, the accelerated growth of direct-to-consumer genetic services

highlights the need for informed decision-making.

"To realize the benefits of genetic technologies and protect against potential harms, the education of healthcare professionals, the public health work force, and the general public is critical. For these reasons, the Secretary's Advisory Committee on Genetics, Health, and Society has formed a taskforce to build on the findings of the Committee's 2004 resolution on genetic education and training of health professionals."

Our draft charge then, following these aims, was one that has been modified by the Committee over the last few months. On the screen you can see the changes but in your booklet you will just see the final revised one. I will read this out loud as well. This is the draft charge that will give us our marching orders.

"The taskforce is charged with developing a plan to identify the education and training needs of health professionals, the public health work force, and the general public in order to optimize the benefits of genetic and genomic services for all Americans. This plan will also outline the steps required to meet these

needs and evaluate the efficacy of educational and training efforts. This plan includes but is not limited to the following activities:

"1) Assembling evidence to determine which recommendations from the 2004 SACGHS education resolution were implemented and which ones require additional efforts;

"2) Identifying the education and training needs specific to genetics and genomics for healthcare professionals;

"3) Identifying the education and training needs of the public health work force;"

No. 4 got scrapped.

"5) Identifying the education needs of patients and consumers to assist them in informed decision-making about the use of genetic services and enhance their understanding and utilization of results and how these results impact decisions about prevention or treatment;

"6) Identifying effective educational tools that can be incorporated into electronic health records, personal health records, and clinical decision support systems that would enhance the appropriate integration of

genetic and genomic technologies throughout the healthcare system without adversely impacting privacy, access, and work flow. In addition, identify gaps where such tools do not currently exist and develop recommendations on how to address these gaps;

"7) Assessing the use of evaluative research methods to determine the efficacy of genetics and genomic education and training." No. 8 got scrapped as well.

What I would like to do is hold your thoughts about any changes you might want with those until I go through some of our activities to see if that informs some of your comments.

The group had a conference call in March. We discussed these new changes of limiting the focus and broke ourselves up into three workgroups focusing on that narrower scope. We were going to focus on health professionals as one group, public health providers, and consumers and patients as the third group.

Chairs were selected for each of those subgroups. George Feero is heading the group with the health professionals, Joseph Telfair is heading the group with public health providers, and Vince Bonham is heading

the group with consumers and patients.

Each workgroup then met on conference calls with their own group. The whole committee was then divided into these groups, and each group met independently to talk about their own action plans, as these were seen as fairly independent.

Then on June 3rd, about a month ago, the chairs and I and Cathy Fomous had a common conference call to see if we could integrate the activities. We came up with an action plan.

The main part of the action plan of course is to produce a report -- we are aiming for 2010 -- that will identify the gaps and make recommendations to address them.

We developed an integrated framework for how to achieve these goals and the decision was made at that point to present to you using a clinical case model to highlight all the needs of the various groups. The reason we chose a clinical case model for this was that we were looking for some way that could integrate all the different perspectives. We wanted to have a way of telling the story about what education and training is

needed and the gaps in a more compelling or evocative way than just writing up a list of recommendations or competencies.

So we came up with a case model way to put a face on the experiences of the various groups, coming up with specific cases that would highlight different lenses that would be used to look through these story lines.

The frameworks that we have chosen have a couple common themes. They will each need to address the needs of the various audiences. We are trying to identify different types of testing, different stages of testing, and different settings, and then how the education or training can best be provided and evaluated in meeting all of these needs.

We came up with an initial list of seven potential case studies that we think might meet those needs and help us highlight the educational and training needs of the three groups we have identified. These are patient diagnosis of a single gene disorder, a family history of a common disease, a case with a newborn screening situation, some pharmacogenomic testing, direct-to-consumer testing, population research, and

media reporting of research results, and designed a case study that highlights each one of those situations. These are in draft form and open to discussion.

Each workgroup designed their own plan for how they want to address their needs for their own specific group. You have the longer versions in your booklet, but [I will] just highlight a few of them.

The Health Professionals Group is planning at this point to start with summarizing the literature and then mapping the existing federal ecosystem, with a plan of doing a survey of key professional organizations to identify their priorities.

The Public Health Provider Group is approaching it at this point by identifying a subset of public health providers to do an assessment of their needs. They plan to review competencies and then assess how the competencies are being met or what gaps are in there.

The Consumer and Patient Workgroup is also starting with a literature review and mapping existing activities and then consulting with experts in the field of genetics and education to identify the gaps.

The next steps of our taskforce or the

workgroups will be executing their action plans. We are hoping to have draft findings by spring of 2009 so we can assemble a draft report for public comment by next summer and the revisions and final report by early 2010, which is fairly ambitious, but that is what we are aiming for.

I would like to lead a discussion on getting a consensus on the two documents that we showed at first. Now that you understand the scope of the group, see if you think that those two documents represent accurately what we should be doing. The first one is the draft charge. Paul.

Discussion

DR. BILLINGS: I have a couple of questions. I was particularly struck by the creation of a public health work force group, or subgroup, or whatever you are calling it, distinct from health professionals. Can you talk a little bit about how that came about and why that separation was made?

DR. McGRATH: Joseph is head of that group. Unfortunately, he left. But we can add the rest of the committee members with it.

It was identified that the healthcare providers

were point-of-care persons, physicians, nurses, genetic counselors, that whole group of point-of-care. The public health providers were more like state officials involved in things like newborn screening policies and things like that. Does that make a reasonable distinction?

DR. BILLINGS: So, if I was a public health physician, I would be a healthcare provider and not a public health work force person?

DR. McGRATH: That is why it is one committee instead of three. That is why we will be using case studies. There is going to be overlap. You may wear one hat in one situation and another hat in another one and have different educational needs for different ones. If you were doing newborn screening, you would have to know a lot more about state policies and things like that versus if you were providing care at a community clinic. That was the thinking. Does that make sense?

DR. BILLINGS: I think if you are going to include broad constituencies outside of, let's say, traditional providers and patients, then you have hospital administrators, you have legislators who are

writing legislator, you have judges doing healthcare law. You are opening it up to a larger group. I'm just curious how you are thinking about the scope of it.

DR. McGRATH: Of that one group?

DR. BILLINGS: Yes.

DR. McGRATH: That last group you just listed is one that we eliminated last time, but we did keep it in public health people.

Any other thoughts?

DR. AMOS: We have heard a lot from industry this morning, different companies. It seems to me that there may be some need to educate up and coming new companies on what are the expectations for scientific rigor that is going to be required for the general genetics community to accept their technologies. Was there ever any discussion about working with industry?

DR. McGRATH: I think in the early discussion -- and those of you who are here, jump in -- that was in a long list of groups that could easily be included. We kept coming back to point-of-care notions and limiting it to that. That was just a decision made. The line had to be drawn someplace.

DR. AMOS: I just think that you might actually remove some of the roadblocks and actually may be able to be a part of the process of getting more clinically relevant, useful diagnostic tests out there by working with industry closely.

DR. McGRATH: Sherrie first.

DR. FITZGERALD: Is this -- oh, I'm sorry. What?

DR. McGRATH: You are not Sherrie.

[Laughter.]

DR. FITZGERALD: I'm speaking for her. No, no.

DR. HANS: Just a quick comment. I'm struck with the Public Health Providers Workgroup that perhaps you don't have the range of expertise that you need on the group. You might think about trying to get some additional members on there from outside the current committee, either from CDC colleagues who are involved in the education of public health providers or groups like the American Public Health Association.

It is a particular diverse group of practitioners, and I think you need that expertise on the workgroup itself in addition to contacting those groups

and getting information from them. I think there is a knowledge and understanding that isn't captured in the current workgroup.

DR. McGRATH: That is a good suggestion. We had made a decision, but we can certainly revisit that, of keeping the workgroup to that size and having a really robust communication using people like that as consultants rather than having them on the group themselves. It is something to revisit. Thank you. Yes.

DR. FITZGERALD: You have DTC down here, though, under different settings. So you will be addressing that issue?

DR. McGRATH: Yes. I was just thinking about adding a response because the idea of the case study around DTC is it is from the lens of the consumer. The case study will be of a person going through that experience. But the way we are envisioning writing it, they will come in contact with various people who also have educational needs. That will allow us to cast that web a little bit wider. That is when I was thinking maybe that is the place to bring in some of the industry

perspective but not as the sole focus. Is that what you were getting at, Kevin?

DR. FITZGERALD: To some extent. It is not just direct-to-consumer testing, though.

DR. McGRATH: Right, right, right. One more. Rochelle.

DR. DREYFUSS: I have a very tiny quibble with the original statement of goals. You used the words "increased understanding of genetic testing" and then you talk about the need for education. If we understand it more, do we need the education? You might just want to say an increase in production of genetic information rather than increasing understanding.

For somebody who has never seen this before, it is kind of confusing.

DR. McGRATH: Good. Thank you. Any other comments so we could reach consensus on those two?

DR. TEUTSCH: With those changes I assume that we have consensus on the charge. The one thing that we of course have to still pick up is the information that we get from the priorities process. Obviously, Paul is going to talk a little bit about that as we get back to

that. But there are issues there that we will be looking to this committee to incorporate as well.

Cathy?

DR. FOMOUS: Rochelle, just to go back to clarify what you are wanting, this is in the paragraph that talks about the specific charge?

DR. DREYFUSS: Yes. The fourth line down. I just saw it on the slide.

DR. FOMOUS: I'm just trying to find where you want the change or what you want exactly.

DR. DREYFUSS: I don't have it in front of me. If you could just go back to the slide of the charge. It was right at the very beginning. Keep going back. "Leading to a better understanding of disease."

DR. FOMOUS: Oh, the very first sentence.

DR. DREYFUSS: Yes. It just looks like we all understand it.

DR. FOMOUS: So, what would you prefer?

DR. DREYFUSS: "Better information" or "more information." Maybe it is fine, but it looked to me like if there is better understanding why do you need more education.

DR. FOMOUS: So it is leading to more information about disease processes.

DR. FROSST: You could probably sub in the word "insight" in there.

DR. DREYFUSS: Yes, that's good.

DR. FOMOUS: I didn't hear that. Put "insight"?

DR. FROSST: Use the word "insight" instead of "understanding."

DR. DREYFUSS: Thank you.

DR. TEUTSCH: All right. Very good. Thanks so much, Barbara. We appreciate your doing that. You will have your work cut out for you.

Now we return to yesterday morning's discussion on the priorities and, obviously, a bit of the discussion that we didn't have this morning on the personalized genomic services. We will have Paul lead this. Sylvia will chip in as we need to. Paul.

Continued Discussion of Plan for Next Steps in Priority-Setting Process

Paul Wise, M.D, M.P.H.

DR. WISE: Thank you very much. The first

thing to recognize is that we have already achieved what we had set out for this Committee to achieve for this session, which, number one, is to review and approve the process that we have been using to set priorities, and number two, general consensus and some very helpful suggested revisions to the categories worthy of further exploration as issue briefs as part of the priority-setting activities for this Committee in the fall, setting up decisions that will have to be made at the December meeting.

There are obviously some time rearrangements that were required in shifting gears a bit for this discussion, but in fact it makes quite good sense to collapse the discussion of these priority setting activities with the discussion of the personalized medicine and direct-to-consumer genetic testing issues basically because they have tended to converge in the sense that our discussions yesterday clearly identified these areas, personalized medicine and DTC, as very important issues for this Committee to address and perhaps to address in a very focused way in the years to come.

Also, there was very much the sense yesterday that we want to make sure that we act quickly on at least one, perhaps more, of these central issues to address during a time of transition these kinds of issues, that converging with the obvious need to discuss in some detail the presentations that were made today.

My suggestion is that as we move forward with the discussion we clearly address the issues that were presented as part of the conversation in today's sessions but we do so with an eye on how we should address personalized medicine and direct-to-consumer genetic testing as a Committee. We [should] address it, consider it, and discuss it with an eye on how it should fit into our priority setting activities over the next few months to ensure that we have a voice at a critical time of transition but also that we have a thoughtful, aggressive voice in setting that agenda at a time that is particularly important and that our voice is strategic in nature.

Let me just open the conversation up at this point to any comments or guidance. Yes, please.

DR. AMOS: Yes. This is my question from

before. Actually, it is a comment. I want to talk about standards a little bit. I think Secretary Leavitt made a very important point as to the competence in the science. I think that what I'm struggling with, and I think most people would be too, is the different companies that are offering different things and the rigor of the science.

The general public doesn't understand that just because you repeat something 16,000 times, your precision of your assay may be really great but it may have no relevance to what is really there. With genomic testing it is a little different. It is a little cleaner than proteomics or something like that.

But at the same time, these methods have not been rigorously evaluated. I will give you an example. In just a "simple" diagnostic test for troponin for MI, we ran a round robin of all the different companies to determine what was the absolute value that each of these diagnostic tests that were FDA-cleared, marketed, and being used in the clinic all the time. I think it was about 10 companies that we ran. There was about a 130 percent CV in the results.

The AACC saw that. They asked us to develop a

standard for troponin. We developed a complex troponin-C standard that brought the CV down considerably to something a little better because the companies were able to recalibrate.

That has not been done for most diagnostic tests. It was done for cholesterol. It was done for calcium. NIST has about 30 clinical chemistry standards that are out there and we work with the Joint Committee on Traceability of Laboratory Medicine, part of the International Bureau of Weights and Measurements, to try to develop ways to harmonize results across diagnostic testing.

I think there are about 140 or so standards that are available internationally for different diagnostic tests, but there are thousands of different diagnostic tests that are run. So from one standpoint, what is going on with this technology is fairly consistent with what is going on in the rest of the field of diagnostics.

So, how do we, as a Committee, try to interject some sound science in this to enable people to make good decisions?

I will make one personal comment with regard to what Kathy Hudson said about making sure that people who are competent and know how to use the information have the test and can take action. To Kevin's point about the father whose kid with cancer was given 44 different drugs, I have had firsthand experience in that. I'm all for information. I was able to use information off the Internet to save the life of my daughter, after having gone to all the great medical institutions in the State of Maryland [where] they couldn't figure out what it was.

I'm all for information, but I guarantee you that if it wasn't for the fact that I could not prescribe medicines myself I might have killed her. When your kid is in a situation like that, be it genetic or anything else, you are just absolutely grasping for information to try to do something to help your kid.

A person who has that information should not be their own physician. That is my personal statement.

DR. TEUTSCH: Thank you. Comments or questions? Kevin.

DR. FITZGERALD: I'm curious. I understand the process and all. Have you already gotten a sense of

different categories you are going to put some of these topics in, considering whether they are going to be large-scale reports or more targeted kinds of, I don't know, white papers or letters to the Secretary or something? Is that still open?

DR. WISE: That is still open. Our approach was not to define what would be the most appropriate, effective action steps but rather to define what areas of content were likely to be of greatest importance to the Committee's work over the next few years.

I'm pretty confident that our general sense was that personalized medicine and direct-to-consumer issues should be part of that deliberation and would be included.

Now, how we approach that I think is really the focal point for this conversation now. We don't have a lot of time, but the hope is to provide some guidance to the various members of the various taskforces, particularly ours, to what would be the most appropriate way to address these issues.

Now, it may be that the most appropriate focus of the work for our group and related groups over the

next few months is merely to articulate what in fact are the central questions that are likely to be most important to this group moving forward. That may in fact be bringing in the best science. There are other tensions that we have heard.

For example, we have heard quite a bit about the push in modern medicine for greater and greater standardization in clinical decision-making, getting clinical discretion out of the encounter. But we have greater and greater standardization coming, smacking head on with what we are calling personalized medicine, which implies a grave departure from standardization. Everything is personalized.

We have a clash between a culture of regulation in health care and a culture of regulation in IT. What we heard today is really IT.

So I could see our work would be, over the next few months, really articulating what the central strategic questions are for this Committee, not in general but for this Committee, and bringing it quickly back to the Committee for further work. Paul.

DR. BILLINGS: Paul, one of the themes that has

seemed to me to come up in the last two days more clearly than before, and was certainly being made earlier in this discussion, was around the issue of standard setting.

Now, we have talked about standard setting specifically in the direct-to-consumer motif, but actually, standard setting of course is broad and goes for all aspects of the genomic and genetic enterprise. It could go for the translation of evidence from association studies into clinical practice. It could go for standards for how you evaluate when a methodology like sequencing is appropriate in the clinical setting. It could go quite broadly. It is a theme.

I was thinking particularly of what the Secretary said about things that are valuable to him. A committee like ours talking about standard setting, even as we instructed FDA in our last meeting, we could also help them with their standard setting.

I wonder whether that is a theme somehow that we ought to incorporate more broadly in one or more of these topic areas.

DR. AMOS: Paul, I just want to comment on that. You said that personalized medicine is not

conducive to standardization, but you have to define what you mean by that. What I'm talking about is actually standardizing the measurements, and there are ways to do that. These measurements could be used universally.

I'm talking about establishing measurement infrastructure, standard reference materials, standard reference data, standard reference methods, that will enable people to actually do direct comparisons over time and space of their measurements. Those are critical.

DR. WISE: I would agree. I would just point out that many people talk about standardization [not as] standards used in the laboratory but rather standards of use in the clinical encounter. So it is very helpful that you point out these distinctions. It may be that we need to address both or pick and choose. But again, articulating what the central strategic questions for this Committee really are I see as some of the work that will need to get done over the next few months.

Muin, do you have a comment?

DR. KHOURY: Since we don't have that much time, Steve, do you want to say something?

DR. TEUTSCH: It seems to me that some of this

is going to get fleshed out in the issue briefs as we get through each of them. I think our task for the next half hour is, we basically had clusters that we agreed to. Are there any that we need to move on? Some of them are going to move to the Education Group that they can begin to act on.

Are there others here that we feel we can tease out that should move separately from the overall priority process, [while] obviously integrated with it, because we believe that they deserve, if you will, a more rapid, more in-depth look between now and December?

I see Mara and then Kevin. Muin, I'm sorry. Do you want to integrate that first?

DR. KHOURY: No, it's okay.

DR. TEUTSCH: So Mara and then Kevin. I'm sorry.

MS. ASPINALL: I'm going to suggest, consistent with the discussion yesterday, that the DTC personal genomics issues are ones that we should move on immediately. They came up high in all of the voting relevant to a lot of people, [as evidenced by the] standing room only [audience] today, and are, I think, a

very relevant issue.

I would separate those DTC issues from personalized medicine more broadly and really would suggest that the personalized medicine and personal genomics continuation of what we started today would be one of the issues that is a priority moving forward consistent with the process -- I guess I'm going out on a limb here -- that we would prioritize as one of the issues to discuss.

DR. FITZGERALD: Just following up on that, I agree DTC is obviously going to be very, very important. Maybe we need to break that out from personalized medicine. My sense was there are a lot of issues embedded in DTC, and that may require a larger, more broad, comprehensive report.

Maybe we could break out some of the issues that were highlighted, ones I think we have already addressed in previous reports which will obviously be a part of any larger reports that come down the pike on personalized medicine or DTC: issues like informed consent, privacy and confidentiality; issues like coverage and reimbursement; and issues like clinical

utility. Set some kind of clear delineation of what we are talking about in those areas in response to questions that have come up or issues that have arisen since the latest rounds of reports even just a month ago.

That I think we could do in a brief, focused period of time. DTC itself, in at least my sense from today, is fairly complex. That may require a more in-depth kind of stroll.

DR. BILLINGS: I would second what Mara said about separating topics of personalized medicine from DTC. Personalized medicine is, in my view, quite a different kettle of fish than all the issues that are brought up by DTC. That is one thing I would want you to do.

DTC, by the way, isn't just one thing. We had several models of DTC up at the podium there today. Aside from reviewing what currently are the controls and standards of the activity, I'm not sure we can get anything done in six months on DTC, actually.

DR. WISE: Muin. I'm sorry. Gurvaneet.

DR. RANDHAWA: This is a process question because I think we are coming up with topics without

having a list of the topics we agree we will be working on. Are we thinking of collapsing some topics together for issue briefs. Are we going to separate some things for higher priorities. That might be useful for us as a starting point.

DR. WISE: We could put up the slides. Basically, the comments and suggestions from yesterday have been attached to the different categories so that when the issue briefs are put together those are part of the consideration.

I don't think there was a sense that we should be collapsing a lot into what really started off as a relatively small group of potential issue briefs but that there may be some rearranging or inclusion of some issues that were suggested yesterday that were not on the original clusters that I presented. But it didn't appear to be anything major. Clearly, we will make it available to everybody so you can see.

DR. RANDHAWA: The reason I'm raising that point is, if we wait for the issue briefs, we will be waiting for the next meeting. I think part of the discussion we had yesterday was shall we act in the

interim on one or two high priority topics or issues. If we have a sense from the group in terms of what are those more or less central issues that we should immediately move on, then that might help us and we don't have to spend time making issue briefs on them.

DR. WISE: If it is the sense of this group, then we will do that. It sounds like a suggestion has been made that we see direct-to-consumer genetic testing, at least initially, as somewhat distinct from use of genetic testing in personalized medicine. We can certainly conform to that.

Then we would move very quickly, as best as possible, to articulate some proposed approaches and get it to the Committee long before December so that we could begin to make some headway on these issues that we expect will be voted as high priority issues in the December meeting and we don't just wait around to do that. Muin.

DR. KHOURY: I guess December would be post-election. Essentially, this is our last meeting before the new administration, or maybe it will be in limbo for a while. Coming back to the list of eight clusters -- and I wish you could put them up -- genetics, healthcare

reform, ensuring the clinical utility of genetic information, public health applications, consumer access to genetic information -- that is where DTC fits in -- informed consent, coverage and reimbursement, education, then genetics, minorities, and health disparities, we have already one taskforce that is doing its work on education. Another one is Evaluation. What will happen?

MS. ASPINALL: We have to figure it out.

DR. KHOURY: We have to figure out what to do with that. Then our job is finished, essentially.

So, are we just buying time between now and December so that the issue briefs can be developed and then we formulate our point of attack for the next administration? Is that what I'm hearing?

If that is the case, then I think we may be missing a couple of opportunities for more immediate action. I don't think the last couple of days' worth of discussion should go unnoticed by this Committee. If anything, at the minimum the Committee could, or should, consider writing a letter of some sort to the Secretary expressing some kind of issue with these personal genomics, if you want to.

The other thing is, three years ago a group of feds, like FDA, CDC, and the FTC, put together some consumer alerts. That was prompted by discussions of this Committee as to what the federal government should do.

In other words, you guys can decide what you want to do. You can bide time while the issue briefs are being developed and we can discuss things in subcommittees and/or act on a couple of things. They don't have to be big things but more placeholders at the end of the administration.

Now, mind you, there is the Oversight Report, the Pharmacogenomics Report, and a whole bunch of other products that this Committee has put in front of the federal government, which is pondering what to do with it. I'm trying to push us to do more rather than less.

DR. WISE: Let me just respond. I have Robinsue next and a few others. Obviously, Steve can talk whenever he wants.

I would not characterize what we are suggesting or what we would like to do as buying time. It is quite the opposite. Number one, we have an arena of past

activities, past proposals, and past work that has not been acted upon by this administration. There may be elements of those things that we want to push in a variety of different ways in the very near term. That is being discussed.

We also have our issue briefs in the eight general areas that we are going to work to move ahead on. But again, there may be a few, probably one or two, like what you suggest and we have been hearing about the last couple of days, that deserve closer, more intense attention. We would then utilize the education ones by the Education Committee and perhaps the personalized medicine and/or the direct-to-consumer genetic testing by the Evaluation Committee or a new group that might be put together to take on one of these, depending on what decisions would need to get made.

But the idea is that we would utilize whatever infrastructure already exists or create whatever new infrastructure exists, to move these issues forward quickly connected to this priority setting process. We would never buy time.

DR. TEUTSCH: A couple things. One is I think

we are trying to get ourselves positioned for the next administration. One of the things that I have asked staff to do, and hopefully we can get agreement from all of you that we should actually do that, is to pull together all the recommendations that we have made historically so that we can have them in front of the new administration. You will get to see a letter in December to make sure that we have the right issues highlighted so that we can move forward with that.

I'm hearing that there is a desire to move reasonably expeditiously on at least a couple of the other issues that we have heard about here: the personalized genomic services and probably DTC. We are already pretty well positioned to take on that. The Evaluation Taskforce we already know has a good name. That can begin to take on that issue. We could form another taskforce if people would like to deal with the DTC issues, if that is a priority that we think we need to get in a more concrete way more than we can do in just an issue brief before the December meeting.

That is one way we could proceed if people would like. If they have other priorities, we can do

that, too. But that is one suggestion about how we might begin to move this so we are a little bit more prepared to actually take action at least beginning in December.

DR. WISE: Robinsue, do you have a comment?

DR. FROHBOESE: Thank you. The comment I was going to make has already been made, so I pass. Thank you.

DR. WISE: Paul.

DR. MILLER: I just want to reiterate Steve's idea and go one step further. I think we can have staff pull together the pending recommendations from the other reports and put it together in an annual report or in a memo from the Committee that goes both to the internal HHS transition committee and that is part of the process.

Not that I'm giving out jobs, but I think it would be helpful not just to pull out the pending recommendations but to somehow prioritize them. Group them in a way that they become really useful and helpful. We heard from the Secretary today about the executive summary. If it is going to be a four-page memo of nothing but bullets that this little Committee sitting in the corner of HHS wants the new Secretary to go through,

it is going to go in the pile.

But to the extent that we can really shape those recommendations [by] prioritizing them in terms of short-term and long-term goals, low-hanging fruit, however we do it, but to really present those recommendations in a way that will become particularly useful for the transition team for the incoming administration, I think that would be really valuable.

DR. WISE: Mara.

MS. ASPINALL: I would also agree. To go back to the comments about doing DTC in six months, prioritizing it now and setting the priorities for the next administration to focus on may not be the be all and end all that we do on DTC. It is not easy, so it would be some real work. But I do believe we can, between now and then, prioritize the issues within DTC to be able to identify what we believe HHS should be looking at going forward.

That doesn't say that after that we don't have a fuller report on other issues. I think it is very consistent with what Steve said about going back. We are giving them, as Paul said, the executive summary. This

is what we have done in the past and this is what we think your high priorities are that haven't been resolved that we still think are out there.

In terms of new issues, here are the new issues you see, but we don't have all the answers now. We just want to make sure in the first 30 days of the new administration that it is on the radar [of the transition team] and SACGHS is looked at as a proactive, up-to-date, current organization that can help them look at it. So it also forms the ability to say come to us, we would like to participate.

DR. TEUTSCH: Listening to what Paul just said about putting together a report, it is not just a compendium. It is going to be structured and focused so that it has impact. There is a lot on your plate already. Is that something that we should be incorporating into this, or do we need to tease that out?

DR. MILLER: I thought it made sense given the clustering.

DR. TEUTSCH: Yes. You said as a basis it needs to be coordinated. We could form another group to actually take on the task because it is taking the

historical stuff and moving it. What is your sense of that?

DR. WISE: My sense is that I think it is appropriate for our committee to do it, and I will do my best. However, it will require significant staff support since I haven't been here for any history.

[Laughter.]

DR. TEUTSCH: We will get revisionist history.

DR. WISE: That's right. I could make it really interesting.

[Laughter.]

DR. WISE: I think that it is precisely the kind of aggressive, strategic voice that needs to come from this Committee during the transition period. I think our committee will work with the other committees and certainly with Steve and the staff to put that type of voice together in the short term. Thank you, Paul.

Kevin and Michael.

DR. FITZGERALD: Just quickly, following up on what Mara just said, I don't think it is going to be onerous to at least raise certain issues like we heard today. Again, much of this is already indicated in

earlier reports. In order not to reinvent the wheel, what I would recommend, too, is talk to Andrea and talk to Marc and other people on the other reports so that we can potentially pull out succinct pieces.

We are talking about standards in the Oversight Report. We are talking about clinical utility in all of the reports. We are talking about direct-to-consumer advertising in the Oversight Report. All these things are already there. All we need to do is, if we are going to put a letter together, just probably boil them all down and focus on raising them.

MS. ASPINALL: I think that is right, but I'm talking about a slightly different tweak on that. Do exactly as you said and highlight the issues. The new administration is going to have tons to read and lots to do. We just want to get to the top of the list and remind them of what we have done so they don't ask us to redo it, et cetera. There is a lot of overlap in people, so it is not as if we are starting completely fresh.

I would still suggest DTC consumer genomics wasn't fully raised in the past reports and that we add that to at least the priority list so it includes some of

the key issues from the past -- we talked about reimbursement and oversight today -- with maybe at least one new issue at the same time.

DR. WISE: Thank you. Michael.

DR. AMOS: The thing that impressed me over the last couple days is Muin's comments and Jim's comments. All the geneticists around the table have specific comments about the science that is being used for the direct-to-consumer testing. I would think a short statement from the Committee stating the validity of the science that is being used. Compare it to good science or bad science, whatever you want to say.

But [talk about] is this good science and what are the issues. We heard from Teri today about the whole genome analysis overall. What can people believe based on good science.

DR. WISE: Jim.

DR. EVANS: Believe it or not, I think there is one thing that the whole Committee can probably agree on. I think that says something very powerful about where our priorities are. That is that over and over during the last two days what we have heard is there is a lot of

excitement among the Committee for issues related to personal genomics and DTC. Let's just say what some of these outfits are doing.

But there is also great concern that a bedrock principle of all of ours, which is clinical utility and evidence-based medicine, could get lost in the shuffle. I think that if we are going to highlight something, it is very worthwhile, in an enthusiastic way. Say this has great promise [while] highlighting adherence to evidence-based medicine and not putting the cart before the horse.

I would just throw that in there as perhaps something that deserves a very high priority in a brief letter.

DR. TEUTSCH: It seems to me that, based on this discussion, there is obviously a need to pull together the information we have heard the last few days. Obviously, the Secretary is interested and we can get that to him at least in a form of what we think are some of the core issues, highlighting some of what Jim said.

Maybe what we could do is draft Sylvia into pulling that together, as she pulled together the last session, for us to look at. It would be good to get

something to this Secretary, since it is of keen interest. Then that will hopefully begin to set some of the framing for some of the work that we are going to need to do in more detail later.

DR. EVANS: Not to sound too iconoclastic, but does it make sense to send something more to this Secretary?

DR. DREYFUSS: He could be the Secretary continuing.

DR. EVANS: The whole purpose of this conversation is to get pertinent things ready for the next Secretary.

DR. TEUTSCH: Those would not be mutually exclusive.

DR. MILLER: There may be things that this particular Secretary, if there is something really easy and low-hanging fruit, might want to do on the way out. He might be able to shake one or two other things out.

DR. TEUTSCH: Particularly if there are things that we have already recommended that we can remind him of. Sylvia.

MS. AU: I definitely need volunteers to help

me. All those people I helped write reports for.

[Laughter.]

MS. AU: I volunteer Marc.

DR. WILLIAMS: I'm listening.

[Laughter.]

MS. AU: You just volunteered, Marc. Kevin? Kevin just volunteered.

DR. WISE: Steve, are there other issues?

DR. TEUTSCH: Are you good?

DR. WISE: I'm good if you are good. I just wanted to thank everybody for all your help over the last few months.

DR. TEUTSCH: Those are the clusters. You have them behind you now. You are framed by them, Paul.

DR. WISE: Yes. For the rest of my life.

DR. TEUTSCH: The Committee will be fleshing out the details of what is in them.

DR. BILLINGS: Steve?

DR. TEUTSCH: Yes, Paul.

DR. BILLINGS: If I heard the process that just went on properly, we are going to maybe draft something like a letter on DTC that Sylvia is going to do, right?

DR. TEUTSCH: Right.

DR. BILLINGS: Paul is going to continue in his wise way to do his thing.

There is another topic on this, that being coverage and reimbursement, which has been the focus of a good deal of work by this Committee already again. That is an area which we may want to also make. The Committee has generally been in agreement that reform of the coverage and reimbursement system is a good idea. Might we want to draft something instructive to this Secretary and the next Secretary about that as well?

DR. WILLIAMS: This is Marc. Can I get in?

DR. TEUTSCH: Sure.

DR. WILLIAMS: Okay. Related to the topic, actually, that was just brought up and from what Sylvia was tasked to do and which I have now apparently volunteered to do, it seems to me that we could take the recommendations from the various reports that have been done over the tenure of this Secretary and essentially do a progress report, which is to say where are we on each of these recommendations. Are they still relevant; are they being continued in another workgroup; are there

issues that still need to be resolved; or are there things that are carrying forward.

It seems to me that that would be a very pragmatic document to develop that could be valuable not only for our current Secretary in terms of things that might be attainable within the short time frame remaining but would also be valuable to the incoming Secretary to say here is the work that has been done, what are the things that we want to target going forward.

That is Point No. 1. Point No. 2 relates to a comment that was made earlier that I think is important to address and not let stand. That is the issue relating to standardization versus personalization. These are not incompatible, and they are not antipode. In quality improvement, the idea is to use techniques of standardization called mass customization, where basically you use evidence-based information to customize care to the individual but do it in a very standardized fashion. There are a number of institutions, including ours, that have done this very effectively.

But what this relates to in terms of our current discussion is having the evidence base, as Jim

Evans has just said. So really, I think that the key to personalized medicine will be to use informatically based mass customization approaches that are going to take advantage of robust evidence bases that really let us know what it is we need to do.

DR. WISE: Thank you, Marc. It sounds like we have some good guidance.

DR. TEUTSCH: We have some guidance and we have some of the people on the workgroup. Paul, I think that some of the things that you are talking about, to the extent that they relate to this, we can certainly pull in on reimbursement. There are all the issues that we have discussed on reimbursement for genetic counseling and things like that which are clearly not resolved.

But beyond that, it seems to me we roll it into the larger document that we are talking about next time because, clearly, those are salient issues that are going to be on the table.

Other thoughts and guidance before we wrap up? Just to be clear, Sarah is saying "How many do we have here?"

[Laughter.]

DR. TEUTSCH: We have two letters. One Sylvia is going to begin to draft that is going to try to pull together what we have heard over the last couple of days on personal genomic services. We will try and link that to some of the things that this Secretary can do with the six months he has remaining.

Then we are going to, in a broader sense, go back over all of our recommendations that we have made and begin to look at framing those in a way that we could present them to the new administration. Paul is going to be working on that, along with some of the things that we need to highlight as being new priorities that we believe should be the focal point for them and will hopefully be the focal point for our work going forward.

DR. WISE: Right. Both would have to attend to what Paul Miller suggested in that it is not a whiny laundry list of things.

[Laughter.]

DR. WISE: But the idea is that we have a strong, aggressive, thoughtful, coherent voice at a time that is likely to be highly chaotic.

So I'm done. Do you want to close the meeting?

DR. AMOS: I just have one quick question. Is somebody from the Committee or the staff going to try to probe and find out what would be the best avenue to communicate with the next administration? I think that would be useful.

DR. TEUTSCH: It would be helpful, particularly if we knew what the new administration was going to be before November. But I do think we have to figure out how to best communicate with them as the time gets closer and we have a better understanding of who they are and what their real interests are.

That is in fact why we have tried to delay this process for making final decisions today. Paul Wise could have taken us to the point of casting things in concrete, but we thought we really should be informed by our best knowledge about what the new administration is likely to be interested in and how we might cast things.

DR. AMOS: Because there are people sitting around the table that have some history.

DR. TEUTSCH: Those of you with history, if you could let us know so we can capitalize on that history later on.

What would you like to say, Mara?

MS. ASPINALL: Maybe not today, but just to clarify what, if anything, in the midst of this discussion is necessary from the Evaluation Taskforce.

DR. TEUTSCH: Clearly, in two minutes we are not going to be able to do that. But there are a lot of items that are on Paul's list that we need to revisit and have that discussion.

MS. ASPINALL: We will do that.

DR. TEUTSCH: Genetics and the healthcare system is a large part of that.

MS. ASPINALL: Right. That is consistent with what we have said in the past. I just want to clarify that. We will have the issue brief and the description for the December meeting.

DR. TEUTSCH: Yes, that's fair enough.

Concluding Remarks

Steven Teutsch, M.D., M.P.H.

DR. TEUTSCH: At the next meeting we have a couple of things on the agenda. The main item that Jim Evans has just been waiting to talk to us about again is the Patents Committee, which hopefully will not only have

a good draft for us to look at but also a set of recommendations, options, considerations, whatever they get cast as, for us to wrestle with.

DR. MILLER: To that we will all be naysayers.

DR. TEUTSCH: We will need to review the recommendations that we want to take forward to the next administration, so we will talk about that. Obviously, this time I think we have come a long way in our priority setting process, so thanks very much to Paul. I think we have had a rich discussion on personalized genomic services.

I don't know if Scott Boyle or Greg are still here, but thanks to them for hosting us yesterday at the meeting. Thank you for all of that. That stimulated, obviously, a lot of discussion not only yesterday but again today.

Thanks to Sylvia. That was a terrific session this morning talking to us about how we cast the right balance between innovation and protecting the public, examining the scientific experience, looking at the people who actually provide the services, how they think they are serving the public good, creating business

models, and so forth.

And to Cathy, who I thought did a great job in framing the policy issues for us.

Finally, to Barbara, who helped us with the Taskforce on Education and Training.

I think that's it. We have our next meeting December 1st and 2nd, after the elections. I look forward to seeing everybody there. Obviously, we have lots of work to do before then. Thank you all.

[Whereupon, at 3:03 p.m., the meeting was adjourned.]

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CERTIFICATION

This is to certify that the attached proceedings

BEFORE THE: **Secretary's Advisory Committee on Genetics, Health, and Society**

HELD: **July 7-8, 2008**

were convened as herein appears, and that this is the official transcript thereof for the file of the Department or Commission.

SONIA GONZALEZ, Court Reporter